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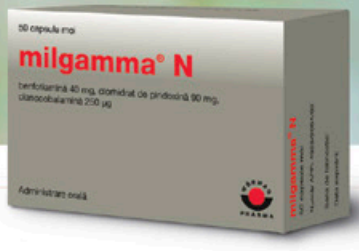

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Editorial

Transforming diabetes care – the Lancet Commission on Diabetes: comments and suggestions for Romania – a position of the Romanian Federation of Diabetes, Nutrition and Metabolic Diseases – Executive Summary

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Motto
In a vulnerable world
People with diabetes are even more vulnerable.
Let's protect them by transforming diabetes care!

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Abstract

In the last four decades, diabetes has become epidemiologically aggressive, threatening the health of millions of people and challenging health systems by increasing costs. Significant changes have been made in many areas of medical and socio-economic life that have become the new world of diabetes. The mission of the lancet commission report is to stimulate the beneficial transformation of diabetes through four major actions. 1. Digital collection of essential data on epidemiology and on the quality of care. 2. Increasing the level of knowledge of doctors and educators. 3. Optimizing the quality of care that can be achieved through adherence to quality standards and the co-participation/activation of patients. It is necessary to gradually approach "precise diabetes" through "personalized management for the right phenotype", where the care of the disease becomes the care of the person with diabetes. 4. Prevention of diabetes and its complications is the last but not the least condition of transformation. The benefits are estimated in terms of increasing the quality of life of people with diabetes, reducing the aggressiveness of the disease, and increasing life expectancy. **Conclusion:** The transformation of diabetes is necessary and possible and the benefits are huge. Let's participate in its achievement.

Keywords: diabetes care, digitalization, patient activation, standards of care

Introduction

The great changes in medicine also include the world of diabetes. The spectrum of diabetes has changed, those who have it have changed, but so have we, those who care for them. Scientific knowledge about the disease, and the strategies of care, has evolved, as well has the society and the political and economic environment. In the face of these changes, which are not always favorable, "thinkers" react and propose solutions. We are living in such a moment. On the 12th of November 2020 The Lancet Commission on diabetes: using data to transform diabetes care and patient life was published [1]. It is an exceptional pragmatic document consisting of analyses, syntheses, and

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simulations related to the diabetes situation in the world but especially in low-income and middle-income countries (LMICs), where 80% of people with diabetes live. Among them are those from Romania. Based on these analyses, four types of recommendations are made regarding: prevention, care, professional development and data collection in the form of registers. They represent an invitation to action. It is estimated through simulations which are the enormous benefits of the action but also the price paid for inaction. The Lancet - Diabetes Commission Report (LDC report) is the result of four years of participation in which 26 international experts in the field of public health, clinical care, epidemiology, and health economics participated. The LDC Report is in addition to the other reports prepared under the auspices of the Lancet, on nutrition, obesity, and malnutrition. All are very valuable contributions to understanding what today not only is the "new nutritional reality", but also the "new reality in the world of diabetes". In this position paper of the Romanian Federation of Diabetes, Nutrition and Metabolic Diseases (RFDNMD) we try to interpret the extraordinary complexity of the messages from the LDC Report, to relate them to the situation of Romania, to analyze the recommendations, and to realistically suggest what can be applied to us. Through this we contribute to improving the lives of people with diabetes in our country, which is part of our professional and moral duty. In diabetology a LOT of KNOWLEDGE is necessary but also the understanding of what we know. Both are "*sine qua non*" conditions for properly incorporating international recommendations and suggesting their sustainable application.

The new reality in the world of diabetes

Based on our professional history, we consider that the world of diabetes includes: the disease and its complications, all people with diabetes, all those who provide their care (doctors and educators), factors that influence care (family, society, organization, and legislative functioning of the health system, local, national and global political and economic determination), the real and sustainable possibilities to achieve it.

Diabetology has a special place, our specialty that ensures both the path of science to the health of patients and the help provided to them to participate in their own care. The LDC defines and analyses all these component factors, without naming the world of diabetes as such. Epidemiological data and the impact (burden) on diabetes, complications, co-morbidities (obesity), as well as mortality caused by diabetes are known from the IDF Atlas published at the end of last year (2020). All are also confirmed in the LDC report. Inequity of diabetes aggression around the world is reaffirmed. We believe that we can already talk about geodiabetes, as a result of geopolitics with proven geo-economic consequences: inequalities in the structures of health care organization, poverty/ wealth ratio, food security, access to education and health care, social discrimination, environmental pollution. As such, the prevalence of diabetes is different, as are complications, co-morbidities, mortality, and effective prevention measures. The complexity, resulting from the analysis and synthesis of data, is amplified by the emergence of the covid-19 pandemic, the synergism with chronic non-communicable diseases (NCDs) or other infectious diseases. All this data requires a transformation of diabetes through reducing the aggressiveness of the disease, which will improve the lives of millions of people. This is how the mission of the lancet commission is defined. The new reality of diabetes foreshadowed from the beginning of the rise of its incidence (in 1980's) but completes its characteristics "before our eyes" as a result of dramatic socio-economic and political changes. These are not only the causes of the new configuration of the world of diabetes but also the conditions of success in the fight to alleviate its threats. To this end, LDC makes recommendations in four sectors, with multiple integrated strategies. We will present them in summary, as well as the suggestions for application in Romania.

Prevention of diabetes

Prevention of diabetes can be achieved through a healthy lifestyle, applied to people at risk using adapted strategies. Detection of people

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at risk is therefore mandatory. The existence of a national prevention program (NPP) that also ensures the legislative framework of implementation is strongly recommended by LDC. In Romania, law no. 249 of 13thof November 2020 on the prevention and early detection of diabetes outlines the main strategies of the NPP, but must be complemented with a set of concrete actions and responsibilities at different levels. The suggestions for Romania are: *Adapting the NPP to the LDC recommendations. *Ensuring the functionality of NPP on the whole spectrum of life. * Priority actions would be the formation of a "smoke-free" environment, along with the other components of healthy environment. *Permanent correlation with other specialties in NCDs, considering that diabetes is at their "root". The annual NCB congress held by RFDNMD under the auspices of the Romanian Academy is an example in this regard. *Initiation and development of the Romanian Obesity Forum which, together with the Romanian Diabetes Forum, offers excellence to the action. *Collaboration with other specialties, governmental and non-governmental organizations, local public authorities, pharma companies or corporations from other fields interested in prevention.

Professional excellence in diabetology

Continuing professional development refers to doctors, educators/nurses by all modern or conventional methods. This involves the participation of universities, professional associations or other accredited bodies. They will provide updated knowledge and ITS application in practice. A somewhat surprising recommendation of the LDC is the development of diabetes as an essential specialty, to ensure the quality of care, the implementation of quality standards based on evidence and professional training focused on "job". As it is known, in Romania the specialty of Diabetes, nutrition and metabolic diseases (DNMD) has existed for 40 years, as well as the scientific societies in these fields: RFDNMD, Romanian Society of Diabetes, Nutrition and Metabolic Diseases, Romanian Associations for Diabetes Education, Romanian Association for the Study of Obesity, and others. In addition, the incorporation into our specialty not only of diabetes, but also of obesity, dyslipidemias, other metabolic diseases as well as nutrition, gives DNMD specialists an overview of diabetes as well as its risk factors (unhealthy diet, obesity), and associated co-morbidities (dyslipidemia, hyperuricemia, etc.). With regard to the education of persons with diabetes, this may be carried out by nurses in diabetes wards and outpatient clinics, provided that they receive initial and continuing training in the field of therapeutic education, as well as a professional position which includes therapeutic education activity.

The suggestions for Romania are: *Organizing the "Platform for permanent professional development" for doctors, related to their qualification: primary care physicians, specialists, and young diabetologists. *Organizing the "Platform for the development of educators" and supporting their participation in training programs through which they can acquire the qualification of "nurse specialized in diabetes". *Development of the DEPARTE project (Determination and Participation in Education), proposed by RFDNMD. This is an educational project in the field of diabetes, obesity, dyslipidemia, and lifestyle science, addressed to patients and the general population. *Collaboration with family doctors, doctors of other specialties and pharmaceutical companies.

Personalized care in diabetes; towards precision diabetology

Optimizing the care of people with diabetes is essential in the effort to change their lives, which is the major goal of the LDC report. The following is recommended: ensuring the necessary structure for care: hospitals, integrated diabetes centers, offices, teams; ensuring their functionality through qualified and professionally trained persons to act in a pre-established programmatic framework; ensuring that quality standards of care are applied in practice; ensuring the material basis necessary for their good functioning; investments to be correlated with the necessary; ensuring access to medicines; ensuring access to training and education, teamwork, improving the

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quality of communication and collaboration with team members: systematic collection of essential clinical data in diabetes registries. Here, the cardiovascular and renal risk will be stratified in the registered patients, in order to apply the personalized organo-protective and integrated treatment.

In Romania, there is a good organizational structure (DNMD network) already in place that needs to improve the quality of functioning. The following essential activities are suggests: *Regaining the status and completing the structure of the clinical centers for diabetes, nutrition, metabolic diseases within the county emergency hospitals and inclusion of all professionals that can contribute to better care (nutritionists, psychologists, podiatrists). *Training of care teams at primary (individual offices) or secondary (outpatient clinics affiliated to hospitals) or tertiary (clinics, bed wards in clinical centers). *Timely planning within the team of the operational flow (diagnosis-therapy). *Establishing quality standards of care for Romania, differentiated according to the level of diabetes care (primary, secondary, tertiary); correlations of the diseases protocols in order to accelerate the adoption of current cardio-renal organo-protective medication in practice (SGLT2i, GLP1-RA). *Promoting clinical judgment for maximum adherence to these standards, along with minimal multifactorial clinical inertia. *Reconsideration of the medical act as the basis of personalized care, at all levels of diabetes care.

Data collection; Diabetes Registry

Digital collection and monitoring of essential data is very useful for real-life analysis in various aspects of diabetes care such as epidemiological assessment (prevalence and incidence), assessment of complications and co-morbidities, estimation of the global cardio-reno-metabolic risk dynamics, evaluation of the dynamics of pharmacotherapy, evidence of participation in the therapeutic education programs, administrative management, assessing the dynamics of successes or the occurrence of failures.

Suggestions for Romania: *Initiation as soon as possible of the NDR (National registry of diabetes). We know from previous failed experiences that it is a real institution whose management is very complex. The establishment of the NDR and Prediabetes is expressly provided in the Law on the prevention and early detection of diabetes in article 14. *Establishment of "pilot" centers or offices where data collection can begin, possibly in the form of thematic registries (for example for: type 1 diabetes, type 2 diabetes in young people, diabesity). *The relevant scientific societies - FRDNBM, SRDNBM, together with the Commission of the Ministry for DNMD can be set up as "advisory bodies" to be involved in the creation of the NDR. *Collaboration with other specialized IT institutions, accredited by the authorities, becomes imperative.

Why is the world of diabetes at the crossroads?

Diabetes is epidemic and threatening and epidemic predictions are even more alarming. The world of diabetes is dependent not only on scientific progress but also on social, political, and economic changes to which are added those of the ecosystems. The new reality of the world of diabetes has two sides, one optimistic, the other pessimistic. The first side would be the result of possible, achievable and effective actions suggested by the LDC report. The other side is the result of inaction or passivity in the face of the epidemic of diabetes and obesity with known consequences on morbidity and mortality.

This is the crossroads where the world of diabetes is now. What should we be doing? The answer is unequivocal: let's transform diabetes!

Conflict of Interest

The authors declare no conflict of interest.

Reference

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Original Research

Shoulder disorders in patients with diabetes mellitus

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Abstract

Background and Aims: Shoulder disorders are common manifestations of musculoskeletal issues affecting patients with diabetes, but get relatively little attention. The aim of the study was to evaluate prevalence of shoulder disorders and its association with glycemic control, duration, and certain epidemiological factors in a section of population with type II diabetes. **Material and Method:** We conducted a prospective study including 32 consecutive patients with type II diabetes and 32 consecutive patients without diabetes attending the outpatient department for shoulder symptoms. Patients underwent physical examination and the proforma and UCLA-m (modified University of California at Los Angeles) Shoulder Rating Scale form were filled. Data was compiled on frequency and contingency tables. Central tendency was measured by mean and standard deviation. For determining the co-relation unpaired t test and chi-square test were used. **Results:** We observed that as the fasting blood glucose and HbA1c values decrease, the UCLA scores increase. Hence, proper glycemic control may help in reducing shoulder pain and complications. There was no relation between the UCLA score and diabetic duration or the age of the patient. **Conclusions:** We conclude frozen shoulder was the most common shoulder disorder in the diabetic group. It is more prevalent in diabetics when compared to non-diabetics. Evaluation of upper limb manifestations in diabetics must include estimation of glycemic control and an examination for other diabetic complications.

Keywords: Diabetes mellitus, frozen shoulder, musculoskeletal disorders, rotator cuff tendinitis.

Background and Aims

Musculoskeletal disorders are commonly associated with diabetes mellitus, but these get relatively little attention [1, 2]. Out of the numerous musculoskeletal complications, shoulder dysfunction and pain due to frozen shoulder and degenerative rotator cuff tear are the most common complaints. They are marked by impaired function, pain, and limited range of movement of the shoulder joint. Mechanisms of these disorders are due to defective microcirculation and non-enzymatic glycosylation processes in and around the shoulder joint. Although it might be related to the diabetic duration, the relationship between shoulder disorders and glycemic control is so far not known [2, 3].

Recognition of the association between diabetes and frozen shoulder facilitates its accurate diagnosis in the setting of diabetes and initiation of proper treatment, which may include correcting glycemic control. Recognition of characteristic musculoskeletal complications of diabetes may be helpful for early diagnosis and initiation of anti-diabetic therapy in delaying the development of complications [4]. The strength of the relation between diabetes and its musculoskeletal manifestations varies in different disorders and is based on other epidemiologic data.

Shoulder disorders are prevalent in diabetics and are usually seen in patients with

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poor glycemic control and other complications of diabetes [5]. Some authors have reported a positive association between diabetic complications, diabetes duration, and control while others did not find any association [6].

Current available treatment includes analgesics and intra-articular steroid injections, along with physiotherapy. In atypical and severe cases, surgical interventions may be contemplated [2].

Hence, considering high prevalence of diabetes in our country and the relationship between diabetes and musculoskeletal complications [7], it is necessary to find out the strength of this relation in our South Indian population and its associated factors. This study was performed to establish the prevalence of shoulder diseases and its association with glycemic control (HbA1c and fasting blood glucose) and diabetic duration, in a section of South Indian population with type II diabetes mellitus (T2DM).

Material and Method

Study design and patients

Once the study was approved by the Institutional Ethics Committee, patients visiting the out-patient department during the study duration of two months having shoulder symptoms with or without Diabetes Mellitus who were willing to participate were included in this prospective observational study conducted at the university hospital by purposive (non-random) sampling patients with neurological and rheumatologic diseases, shoulder trauma, and professions requiring enormous effort of the upper limbs; those who were not willing to participate were excluded. Sample size was calculated by (with 95% confidence interval (CI) level and 80% power) using the formula

$$n = \frac{Za^2pq}{d^2}$$

Where Zα = 1.96 at 95% Confidence Level
p = prevalence (78.5%)
q = (1 – p)
d = 20% of p (80% power)

Laboratory, anthropometric and clinical data collection

We included a sample size of 64 participants—32 consecutive patients with type II diabetes mellitus and 32 consecutive patients without diabetes— attending outpatient department for shoulder symptoms. All participating patients were provided with a patient information sheet and procedural matters were explained to them along with informed consent form. Patients underwent history and physical examination and then the proforma and UCLA-m (modified University of California at Los Angeles) Shoulder Rating Scale form were filled. Information on epidemiological data from both the groups and on anti-diabetic treatment and diabetic duration was collected, in addition to the levels of fasting blood glucose and HbA1c (glycemic control), from the diabetic group. Rotator cuff pathology and subacromial bursitis with impingement was suspected after a positive Hawkin's or Neer's sign. These patients were further subjected for ultrasonography of shoulder. Frozen shoulder was diagnosed by severe restriction of active and passive abduction and both rotations. Plain shoulder radiograph was done in all these patients. Patients were not subjected to MRI imaging as no surgery was planned for any of the patients. The domains in the UCLA scale included: pain (10 points), function (10 points), range of flexion (10 points), and patient's satisfaction (5 points). Physical examination accounted for 20 points out of the total 35 points, and subjective parameters were accountable for the rest of the 15 points [8]. The domains pain and patient satisfaction were determined by interview, and the domains range of flexion and function by physical examination. Interpreting the UCLA Shoulder rating scale, with a maximum score of 35 points, is as follows: >27 for good/excellent, <27 for fair/poor. Excellent/good implies satisfactory results, whereas fair/poor implies unsatisfactory results.

Statistical analysis

Data was compiled on frequency and contingency tables. Central tendency was measured

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by mean and standard deviation. For determining the co relation unpaired t test and chi-square test were used. A statistical package SPSS vers.17.0 was used to do the analysis. $p < 0.05$ was considered significant.

Results

A total of 32 consecutive patients with T2DM and 32 consecutive patients without diabetes attending the outpatient department for shoulder symptoms were included in our study. The non-diabetic patients were aged between 24 to 68 years (median age = 54.5) and the diabetic patients were aged between 42–68 years (median age = 58). 59.4% of non-diabetic patients (n = 19) were females and 40.6% (n =13) were males whereas 56.3% of diabetic patients (n = 18) were females and 43.8% (n = 14) were males. In total the study included 37 females (57.8%) and 27 males (42.2%).

The mean of HbA1c of diabetic patients was 6.934 ± 1.36, the mean of fasting blood glucose was 154.375 ± 77.32 mg and the mean of diabetic duration was 10.969 ± 13.31 years (table 1).

The left side was affected in 37.5% of non-diabetic patients (n = 12), the right side was affected in 59.4% (n = 19) and 3.1% (n = 1) were affected bilaterally whereas in 40.6% of diabetic patients (n = 13) the left side was affected, the right side was affected in 56.3% (n = 18) and 3.1% (n = 1) were affected bilaterally (table 2).

The most common condition seen in the non-diabetic group was rotator cuff tendinitis and was seen in 15 patients (46.9% of non-diabetics) whereas frozen shoulder was the most common condition in the diabetic group and was seen in 27 patients (84.4% of diabetics). This data is highly significant statistically with a p value < 0.001 (table 3).

The mean of UCLA score of non-diabetic patients was 19.438 ± 8.545 whereas in diabetic patients the mean of UCLA score was 17.500 ± 6.4658. This data is statistically significant with a p value of 0.045 (table 4).

The UCLA score has a negative relation with the HbA1c and fasting blood glucose (r = –0.375 and –0.433, respectively), which is statistically significant with p value 0.035 and 0.013, respectively, that is as the HbA1c and fasting blood glucose level decreases the UCLA score increases. Hence, proper glycemic control may help in reducing shoulder pain and complications. There is weak, not significant, relation between the UCLA score and diabetic duration (r = –0.059; $p = 0.747$) as well as between the UCLA score and the age of the patient (r = 0.028; $p = 0.878$). The age of the patient is positively (r = 0.377) and significantly ($p = 0.033$) related to diabetic duration, probably because our study included patients with T2DM who were aged above 40 years. Also, the age of the patient is weakly and not significantly related to HbA1c (r = –0.023; $p = 0.902$) and fasting blood glucose (r = 0.086; $p = 0.642$). The fasting blood glucose was found to have a strong (r = 0.931) and significant ($p < 0.001$) relation with HbA1c, which was probably because the patients in our study had very poor glycemic control (table 5).

Discussion

Shoulder disorders are commonly associated with diabetes mellitus. Frozen shoulder is the most common and disabling disorder. The mechanism of its development is not well explained. It is noted that increased level of blood glucose leads to accumulation of glycosylated products in the joint cavities, collagen and makes them susceptible to damage and degeneration [6, 7].

In our study, we found a high prevalence of frozen shoulder and associated complications in patients with T2DM. Frozen shoulder was the most common shoulder disorder in the diabetic group and was seen in 27 out of 32 patients (84.4%

Table 1: Diabetic history.

Diabetic history	Mean	Standard Deviation
HbA1c	6.934	0.680
Fasting blood glucose	154.375	38.660
Duration	10.969	6.655

Table 2: Side affected ($p = 0.967$, ns).

			Group		
			Diabetic	Non-diabetic	Total
Side affected	Bilateral	Count	1	1	2
		%	3.1%	3.1%	3.1%
	Left	Count	12	13	25
		%	37.5%	40.6%	39.1%
	Right	Count	19	18	37
		%	59.4%	56.3%	57.8%
Total		Count	32	32	64
%			100.0%	100.0%	100.0%

Table 3: Diagnosis($p < 0.001$, vhs).

Diagnosis		Group		Total
		Non-diabetic	Diabetic	
Acromio-clavicular joint osteoarthritis	Count	1	1	2
	%	3.1%	3.1%	3.1%
Acromio-clavicular joint osteoarthritis with shoulder joint Impingement syndrome	Count	1	2	3
	%	3.1%	6.2%	4.7%
Calcific tendinitis	Count	3	0	3
	%	9.3%	0.0%	4.7%
Cervical Spondylolisthesis with rotator cuff tendinitis	Count	1	0	1
	%	3.1%	0.0%	1.6%
Frozen shoulder	Count	9	27	36
	%	28.1%	84.4%	56.3%
Rotator cuff tendinitis	Count	15	1	16
	%	46.9%	3.1%	25.0%
Shoulder joint impingement syndrome	Count	1	0	1
	%	3.1%	0.0%	1.6%
Subacromial bursitis	Count	0	1	1
	%	0.0%	3.1%	1.6%
Supraspinatus tendinitis and subacromial bursitis	Count	1	0	1
	%	3.1%	0.0%	1.6%
Total	Count %	32	32	64
		100.0%	100.0%	100.0%

of diabetics) as compared to 9 out of 32 non-diabetic patients (28.1%) ($p < 0.001$).

Frozen shoulder was present in 12% of diabetics and none of the general patients in a study by Cagliero and Perlmutter [1]. A prevalence of 25% was found in study conducted by Ramchurn et al [5]. In a study by Tighe et al [7], the prevalence of diabetes in patients with frozen shoulder was 71.5% (63 of 88) and it proved that the occurrence of frozen shoulder was two- to four- times

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Table 4: UCLA (University California Los Angeles) score ($p = 0.045$, significant).

			UCLA score	HbA1c	Age	Fasting blood glucose
Diabetic correlations	Duration	r	–0.059	0.158	0.377	0.232
		p	0.747	0.387	0.033	0.202
		N	32	32	32	32
	UCLA score	r		–0.375	0.028	–0.433
		p		0.035	0.878	0.013
		N		32	32	32
	HbA1c	r			–0.023	0.931
		p			0.902	0.000
		N			32	32
	Age	r				0.086
		p				0.642
		N				32

Table 5: Diabetic correlations.

Group	Mean	Standard Deviation
Non-diabetic	19.438	4.2725
Diabetic	17.500	3.2329

more in diabetics than the non-diabetics. The presence of frozen shoulder in patients with T2DM in our study was greater than previously reported and more in diabetics when compared to non-diabetics.

The musculoskeletal manifestations of diabetes mellitus are very prevalent and, although non-fatal, lead to pain and dysfunction, thereby affecting the quality of life [10, 11, 12]. Identification and understanding the correlation between diabetes mellitus and shoulder joint disorders is necessary for enhancing the quality of life of diabetics. Recognition of characteristic musculoskeletal complications of diabetes, its correct diagnosis in the setting of diabetes, and initiation of proper treatment, which may include initiation of glycemic control, delay the development of other diabetic complications [13].

The mean of UCLA score of non-diabetic patients was 19.438 ± 8.545 whereas in DM the mean of UCLA score was 17.500 ± 6.4658 ($p = 0.045$). The UCLA score was significantly lower in diabetics compared to the non-diabetics. The UCLA score had a negative correlation with the HbA1c and fasting blood glucose ($r = –0.375$ and –0.433 and $p = 0.035$ and 0.013 respectively), as the HbA1c and fasting blood glucose level decreases the UCLA score increases. Proper glycemic control may help in reducing incidence of shoulder pain and complications. But there is no correlation between the UCLA score and diabetic duration or age of the patient.

The strength of this study is that it compares shoulder disorders in diabetic and non-diabetic individuals. This type of study was not reported from this part of the world. The weakness of the study includes smaller samples and selection criteria, purely based on clinical parameters. A larger sample size with a looking out for more outcome measures would have provided better information.

Conclusions

We conclude that there is a very high prevalence of shoulder disorders in the studied population with T2DM. Frozen shoulder was the most common shoulder disorder in the diabetic group and was seen in 27 out of 32 patients (84.4% of diabetics) as compared to 9 out of 32

non-diabetic patients (28.1%). The presence of frozen shoulder in diabetics in our study was greater than previously reported and more in diabetics when compared to non-diabetics. The UCLA score was remarkably lower in diabetics as measured against the non-diabetics. The UCLA score had a negative co relation with the HbA1c and fasting blood glucose, that is as the HbA1c and fasting blood glucose level decreases the UCLA score increases. The information gained by the study can be utilized for the early diagnosis and management of shoulder problems in diabetic patients. Evaluation of upper limb manifestations in diabetics must include estimation of glycemic control and an examination for other diabetic complications like retinopathy or nephropathy.

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Conflict of Interest

The authors declare no conflict of interest.

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Original Research

Alternative antibacterial therapy of Methicillin-resistant Staphylococcus aureusin patients with diabetic foot and sepsis

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Abstract

A total of 210 patients with diabetic foot and sepsis who were treated in the purulent-septic center of Zaporizhzhya, Ukraine, were examined for the period of 2007–2020. All patients had type II diabetes mellitus, with a duration of 12.6 ± 2.7 years and an age of 56.8 ± 2.5 years. The diagnosis of sepsis is established according to the criteria of Sepsis-3 (2016). The complex of therapeutic measures included the mandatory use of antibacterial drugs, which was preceded by a microbiological study of biological material (blood and wound discharge). Gram-positive flora was detected in 118 (56.2%) patients and prevailed over gram-negative 81 (38.6%), anaerobes were detected in six (2, 8%) patients, and fungal flora in five (2.4%). Among patients diagnosed with Staphylococcus aureus 52 (100%), Methicillin-resistant Staphylococcus aureus (MRSA) prevailed with 38 (73.0%) ($p < 0.05$). We have identified a pattern that allowed us to categorize patients with MRSA into four groups according to similar sensitivity to antibacterial drugs, which received the conventional designations MRSA type 1; MRSA type 2; MRSA type 3; MRSA type 4. Moreover, MRSA type 4–3 (7, 9%) of the patient is pan-resistant. The most universal drugs in the presence of MRSA in patients with sepsis caused by complicated DFS are daptomycin, linezolid, teicoplanin, vancomycin, and tigecycline. In patients with MRSA type 1 and MRSA type 2, except standard anti - MRSA antibiotics, aminoglycosides, fluoroquinolones and macrolides can be effectively used as first-line drugs.

Keywords: Antibacterial therapy, diabetic foot, Methicillin-resistant Staphylococcus aureus, sepsis.

Introduction

Sepsis remains one of the most urgent and complex medical and social problems due to the stable increase in the number of patients and high mortality. Every year, the incidence of sepsis in the world increases by 8–13%, which requires huge material costs for the treatment of patients of this category [1–3].

It is known that the mortality rate of patients with sepsis depends on the age of the patients, the type of pathogen, the condition of the focus of infection, concomitant pathology, and directed antibiotic therapy (ABT) [4–7].

The existing basic recommendations of the European Concept for the Treatment of Sepsis (Surviving Sepsis Campaign) clearly state that ABT is the most important component of the

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comprehensive treatment of sepsis. In recent years, strong evidences have been obtained that timely administration of ABT leads to a decrease in mortality and complication rates (evidence category C) [8–11].

Among the problems associated with ABT, the most significant is the development of resistance to β-lactams in Staphylococcus aureus (S. aureus) and other representatives of gram-positive microflora [12, 13].

The frequent clinical inefficiency of ABT is due to the presence of Methicillin-resistant Staphylococcus aureus (MRSA), which leads to a worsening of the course of the disease and the development of complications [14–16].

S. aureus is an important human pathogen responsible for infectious diseases in the population as well as in healthcare facilities. The adaptive ability of S. aureus to antibiotics led in the early 1960s to the appearance of methicillin-resistant Staphylococcus aureus (MRSA). The cause of resistance to methicillin and all other beta-lactam antibiotics is themecAgene, which is located in the mobile genetic element, the staphylococcal cassette chromosome mec (SCCmec) (mobile genetic element, the staphylococcal cassette chromosome mec (SCCmec)) [17–19].

Studies comparing active screening for identification of MRSA carriers upon admission to the hospital (using the rapid molecular test or standard blood culture method) or the lack of screening have shown that the diagnosis of MRSA followed by eradication is a major factor in increasing patient survival by sepsis [20–22].

S. aureus can easily become antibiotic resistant, and MRSA is multidrug resistant. MRSA is a serious problem, as it leads to an increase in mortality, despite the use of expensive antibiotics as a last resource [23–26].

The resistance to vancomycin, the main traditional anti-MRSA antibiotic, is rare, although isolates with reduced sensitivity are found in many regions. Linezolid and daptomycin remain largely active against the vast majority of MSSA and MRSA [27].

Since S. aureus is constantly evolving, it is important to monitor the epidemiology of its various strains, since information at the regional level will help in forming a global perspective [28–30].

Materials and Methods

A total of 210 patients with sepsis, the cause of which was complicated diabetic foot syndrome (DFS) were examined. Patients were treated in the purulent-septic city center of Zaporizhia, for the period of 2007–2020. All patients had type 2 diabetes mellitus (T2DM), the average duration of which was 12.6 ± 2.7 years. The average age of the patients was 56.8 ± 2.5 years.

The diagnosis of sepsis is made according to the criteria set out in the International Guidelines for the treatment of sepsis and septic shock -Sepsis-3 (2016), using the Quick SOFA scale. Thus, after the diagnosis of sepsis was determined, the patients were transferred to the high-risk group and continued treatment in the intensive care unit.

The reason for the development of sepsis was a purulent-necrotic lesion of the foot – an abscess, phlegmon, purulent tendovaginitis, purulent arthritis, gangrene.

According to the classification of the International Working Group on Diabetic Foot Problems (1991), patients were divided into clinical forms – 86 patients with a neuropathic form of DFS and 124 – with a mixed one. According to the WIFI classification (2014), patients had a characteristic of 2(3)0(1)3. The local reaction was characterized by signs of inflammation: purulent discharge, redness of the skin, pain, swelling, local hyperthermia, lymphangitis. Fascia, muscles, tendons, and bones of the foot were involved in the pathological process.

Perfusion of the lower extremities was characterized by moderate impairment of the main and microcirculatory blood flow, the ankle-brachial index (ABI) was recorded in the range of 0.6–0.9. The indicator of the transcutaneous oxygen tension at the foot (TcPO2) was ≥60 mm Hg. Art. All patients had diabetic neuropathy of varying severity.

All patients were operated on, and the complex of therapeutic measures included the mandatory use of antibacterial drugs, which was preceded by a microbiological study of biological material (blood and wound discharge). The qualitative composition of the flora and the sensitivity of the

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isolated cultures to antibiotics were determined using BacT/ALERT media to isolate microorganisms using a Vitek 2 Compact automatic bacteriological analyzer (Biomerieux, France). The technical capabilities of the method allow identification of aerobic and facultative anaerobic microorganisms, except non-spore-forming anaerobic microorganisms, as well as discovering the presence of MRSA. The study was conducted during hospitalization and in dynamics.

Statistical analysis was performed using descriptive statistics. Checking the data for the normality of the distribution was carried out visually by the histogram and using the Kolmogorov-Smirnov test. Given the normal distribution in the analyzed samples, the parameters of the parametric descriptive statistics were calculated in the format M ± m (average value ± standard error of the average value). The significance of differences was evaluated depending on the analyzed data using the Student's parametric criterion. Differences were considered significant at $p < 0.05$.

Results

Primary antibiograms of 210 patients with sepsis made it possible to determine the pathogen and its sensitivity to antibacterial drugs (table 1).

Gram-positive flora was detected in 118 (56.2%) patients and prevailed over gram-negative - 81 (38.6%), anaerobes were detected in 6 (2, 8%) patients, and fungal flora in 5 (2.4%).

The leaders among the pathogens were Staphylococcus aureus – 52 (24.7%), Enterococcus faecalis – 29 (13.8%), Pseudomonas aeruginosa – 23 (10.9%), Staphylococcus epidermidis – 16 (7.6%), Escherichia coli – 15 (7, 1%), Acinetobacter baumannii – 13 (6.2%), the remaining bacteria was less than 5%.

Patients diagnosed with *Staphylococcus Aureus* 52 (100%) are differentiated by the presence of the Methicillin-resistant Staphylococcus aureus gene (MRSA): detected in 38 (73.0%), absent in 14 (27.0%). The amount of MRSA was significantly ($p<0.05$) greater than Methicillin-sensitive Staphylococcus aureus (MSSA).

The pathogen type and invitro sensitivity to known antibiotic groups was studied standardly: β-lactams, aminoglycosides, fluoroquinolones, macrolides, lincosamides, lipopeptides, oxazolidinones, glycopeptides, sulfanilamide's, tetracyclines, rifampicin (table).

Among the patients with MSSA 14 (100%), 13 (92.8%) of them had predicted resistance to ceftazidime. Resistance to cephalosporins of the 1st and 2nd generation was revealed in 6 (42.8%) patients, to natural and semi-synthetic penicillin's – in 12 (85.7%) patients. To protected penicillin's, 3rd and 4th generation cephalosporins, carbapenems – no resistance was detected. The phenotype of resistance to tobramycin from the aminoglycoside group was noted in 100% of patients. A resistance level of more than 50% was detected for drugs from the macrolide group, lincosamides lipopeptides, ciprofloxacin and levofloxacin from the fluoroquinolone group.

The sensitivity level of more than 92% was found in: amikacin, gentamicin, netilmicin (aminoglycoside group), and moxifloxacin (group of fluoroquinolones). In vancomycin, teicoplanin (group of glycopeptides), the sensitivity level is up to 80%.

No phenotype of resistance was detected in linezolid (group of oxazolidinones), trimethoprim / sulfamethoxazole (group of sulfonamides), and all drugs from the group of tetracyclines.

According to the data obtained, MSSA is sensitive to varying degrees: protected aminopenicillins; 3rd generation cephalosporins (ceftriaxone); 3rd generation protected cephalosporins; 4th generation cephalosporins (cefepime); preparations from the aminoglycoside group (except tobramycin); fluoroquinolones; lincosamides; glycopeptides; tetracyclines; sulfonamides (trimethoprim/sulfamethoxazole).

A study of the resistance of Staphylococcus aureus in the presence of the MRSA gene in 38 (100%) patients confirmed its genetic 100% resistance to all β-lactams. A resistance level of up to 50% was found for kamikacin, gentamicin, netilmicin (a group of aminoglycosides). Drugs from the group of fluoroquinolones, macrolides, sulfonamides – sensitivity level up to 30%.

When processing data on the resistance of MRSA, a pattern was revealed that allowed us to categorize patients into four groups that were

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Table 1: The sensitivity of *Staphylococcus Aureus* to antibiotics in patients with diabetic foot and sepsis.

Antibiotics in groups	MSSA	MRSA type 1	MRSA type 2	MRSA type 3	MRSA type 4
β-lactam antibiotics		0	0	0	0
benzylpenicillin	0/1	0	0	0	0
Ampicillin	0/1	0	0	0	0
amoxicillin	0/1	0	0	0	0
Ticarcillin	0/1	0	0	0	0
piperacillin	0/1	0	0	0	0
ampicillin-sulbactam	1	0	0	0	0
amoxicillin-clavulanate	1	0	0	0	0
ticarcillin-clavulanate	1	0	0	0	0
piperacillin-tazobactam	1	0	0	0	0
Cefazolin	0/1	0	0	0	0
cefuroxime	0/1	0	0	0	0
ceftriaxone	1	0	0	0	0
ceftazidime	0	0	0	0	0
Cefepime	1	0	0	0	0
ceftriaxone-tazobactam	1	0	0	0	0
ertapenem	1	0	0	0	0
imipenem/cilastatin	1	0	0	0	0
meropenem	1	0	0	0	0
Aminoglycosides					
Amikacin	1	1	1	0	0
gentamicin	1	1	1	0	0
Netilmicin	1	1	1	0	0
tobramycin	0	0	0	0	0
Quinolones/Fluoroquinolones					
ciprofloxacin	0/1	1	0	0	0
levofloxacin	0/1	1	0	0	0
moxifloxacin	1	1	0	0	0
Macrolides					
azithromycin	0/1	1	0	0	0
clarithromycin	0/1	1	0	0	0
roxithromycin	0/1	1	0	0	0
Lincosamides					
clindamycin	0/1	0	0	0	0
lincomycin	0/1	0	0	0	0
Lipopeptides					
daptomycin	0/1	1	1	1	0
Oxazolidinones					
Linezolid	1	1	1	1	0

(*continues*)

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Table 1: *Continued*

Antibioticsingroups	MSSA	MRSA type 1	MRSA type 2	MRSA type 3	MRSA type 4
Glycopeptides					
vancomycin	0/1	1	1	1	0
teicoplanin	0/1	1	1	1	0
Tetracyclines					
tetracycline	1	0	0	0	0
doxycycline	1	0	0	0	0
minocycline	1	0	0	0	0
tetracycline	1	0	0	0	0
tigecycline	**1**	**1**	**1**	**1**	**0**
Sulfonamides					
trimethoprim/sulfamethoxazole	1	1	1	0	0
Rifamycins					
rifampicin	0	0	0	0	0

Note.0 - no sensitivity; 1 - sensitive; 0/1 - sensitivity 40–80%; the regularity for this group is highlighted in color.

designated: MRSA type 1; MRSA type 2; MRSA type 3; MRSA type 4.

In MRSA type 1, 10 (26.3%) patients, sensitivity to aminoglycosides (amikacin, gentamicin, netilmicin), fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin), macrolides (azithromycin, clarithromycin, clarithromycin, linklinkin), lipopeptides (daptomycin), oxazolidinones (linezolid), glycopeptides (vancomycin, teicoplanin), tetracyclines (tigecycline), sulfonamides (trimethoprim/sulfamethoxazole) are preserved.

MRSA type 2, 9 (23.7%) patients, was characterized by sensitivity to aminoglycosides (amikacin, gentamicin, netilmicin), lycopeptides (daptomycin), oxazolidinones (linezolid), glycopeptides (vancomycin, teicoplanin), tetracyclines (taigetracycline, (trimethoprim/sulfamethoxazole).

MRSA type 3, 16 (42.1%) patients were sensitive to lycopeptides (daptomycin), oxazolidinones (linezolid), glycopeptides (vancomycin, teicoplanin), tetracyclines (tigecycline).

MRSA type 4, 3 (7.9%) patients were pan-resistant.

Discussion

A screening study of blood in patients with sepsis allows to determine the qualitative composition of the flora, sensitivity to antibiotics, and to identify multiresistant and pan-resistant strains. To conduct effective antibiotic therapy it is currently not enough to identify the pathogen, it is important to determine the presence of the phenotype of resistance to various drugs.

Possibly a specific genetic variant of MRSA corresponds to its portrait of antibacterial resistance and sensitivity, with common features, but noticeable differences.

The most effective drugs in the presence of MRSA, in 35 (92.1%) patients, are identified: tigecycline (group of tetracyclines), daptomycin (a group of lycopeptides), linezolid (oxazolidinones), teicoplanin, vancomycin (a group of glycopeptides).

Thus, in some patients with MRSA 19 (50%) type 1 and type 2, in addition to standard anti - MRSA antibiotics, aminoglycosides, fluoroquinolones, and macrolides can also be effective.

Conclusion

1. A blood screening study in patients with sepsis caused by complicated DFS has allowed us to determine the qualitative composition of the flora, sensitivity to antibiotics, and to identify multiresistant and pan-resistant strains.

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2. In the group of patients with sepsis and with diagnosed Staphylococcus aureus, MRSA gene was detected in 38 (73.0%) patients; its number was significantly ($p<0.05$) higher than MSSA.
3. The most universal drugs in the presence of MRSA in patients with sepsis caused by complicated DFS are: daptomycin (a group of lycopeptides), linezolid (oxazolidinones), teicoplanin, vancomycin (a group of glycopeptides), and tigecycline (a group of tetracyclines).
4. In some patients with MRSA, depending on the genetic variant (up to 50%), in addition to standard anti-MRSA antibiotics, aminoglycosides, fluoroquinolones, and macrolides can also be effective.
5. The different genetic variant of MRSA corresponds to its portrait of antibacterial resistance and sensitivity, with common features, but noticeable differences.

Conflict of Interest

The authors declare no conflict of interest.

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Original Research

Complete blood count and cardiovascular risk markers in type 2 diabetes mellitus – findings from a cross-sectional study in south India

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Abstract

Background and Aim: Poorly controlled diabetes leads to various micro and macro vascular complications. Hematological indices can be an independent predictor of cardio vascular diseases risk ratios and associated with a high white blood cell count are comparable to other inflammatory markers. The main aim of the current work was to evaluate the correlation between cardiovascular risk markers with the complete blood count among type2 diabetes mellitus (T2DM). **Material and Methods:** Study population included 105 subjects with T2DM. Age group of the study participants was 40–60 years. Complete blood count and markers such as HsCRP, lipid profile, and Hepatic Enzymes were estimated. Data analysis was performed with SPSS 17. Differences among groups were calculated using t test and/or Mann-Whitney Test for parametric and nonparametric variables, respectively. Chi square test was used. The correlation analysis was performed by Pearson correlation/Kendall's tau method for parametric and nonparametric variables respectively. **Results and Conclusion:** On analysis, hematological parameter shows significance with various cardio vascular risk markers and can be used as biomarker to assess the severity of cardio vascular diseases.

Keywords: Hepatic enzymes, hematological parameters, high sensitive C-reactive protein, lipid profile.

Introduction

Diabetes is a major risk factor for the development of cardiovascular diseases (CVD). Poorly controlled diabetes leads to various micro and macro vascular complications such as coronary artery diseases, peripheral arterial disease, stroke, nephropathy, retinopathy, neuropathy, and oxidative damage to tissues and cells [1–5]. Globally CVD affects approximately 32.2% of all individuals with T2DM and is a major cause of mortality among people with T2DM. Coronary artery disease and

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stroke were the major contributors for mortality [6]. Many biomarkers have been used to predict the inflammation and risk of Cardio vascular diseases. Hematological indices are an independent predictor of cardio vascular diseases' risk ratios and along with a high white blood cell count are comparable to other inflammatory markers like Hs CRP [70].

Cellular elements in the blood are involved in the pathogenesis of atherosclerosis which is due to inflammation and leads to ischemia. The persistent increase in glycosylated hemoglobin as a result of poor glycemic management is associated with the structural and functional changes in hemoglobin (Hb) molecule, the osmotic disturbance, and the cytoplasm viscosity within each cell. All these changes have an imposing effect on any of the red blood cell indices including mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and the cell shape and deformability represented by red blood cell distribution (RDW). These indices are reported as cardiovascular risk markers in various populations [8, 9]. RDW, a measure of the variability in size of circulating RBC commonly used for the diagnosis of anemia, has recently drawn increased attention as a potential biomarker of CVD risk. Researchers have demonstrated that higher or even normal reference range of RDW was strongly associated with increased risk of cardiovascular disease (CVD) events in middle aged and older adults [10, 11]. WBC count is positively associated with increased cardiovascular mortality, mainly from coronary heart diseases [12–15]. Platelets, another element of the complete blood count (CBC), play a key role in the development of atherothrombosis, resulting in cardiovascular diseases in diabetes with respect to altered platelet morphology and function [16].

Since there is paucity of data related to the association of different hematological parameters with risk markers for cardiovascular diseases in T2DM subjects, the main aim of the current work was to evaluate the correlation between cardiovascular risk markers with the complete blood count among T2DM. These tests are inexpensive, widely available, and easy to interpret.

Materials and Methods

We recruited 105 patients, with T2DM reported to Department of General Medicine, ACS medical college and hospital for routine checkup. This study included 48 males and 57 females. Subjects with cardio vascular diseases, recent surgeries, thyroid disorders, end stage renal disease, and any cancerous conditions were excluded from the study. All the participants were provided with the information sheet and informed written consent was obtained. The study was approved by institutional ethics committee.

Demographic parameters such as age, height, weight, and body mass index (BMI), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded for all the patients. After overnight fasting, venous blood samples were collected. Glycemic parameters such as fasting plasma glucose (FPG), HbA1c and complete blood count were estimated by fully automated bidirectional analyzer (sx part differential sysmex XN -1000). Red blood cell indices such as mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and red blood cell distribution width (RCDW), total WBC'S, differential leucocyte count, neutrophil lymphocyte ratio, platelet indices such as mean platelet volume (MPV) and platelet large cell ratio (PLCR) were estimated. Cardio vascular risk markers such as HsCRP, lipid profile which includes total cholesterol, low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), and triglycerides (TGL) were estimated. Hepatic enzymes such as asparate-aminotransferase (AST), alanine transaminase (ALT), gamma glutamyl transferase (GGT), and alkaline phosphatase (ALP) were also analyzed.

Data Analysis

Continuous data were presented as mean ± SD and comparison of continuous data between groups was done by independent t test and the association between the parameters was analyzed using Pearson correlation.

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Differences among groups were calculated using t test and/or Mann-Whitney Test for parametric and nonparametric variables, respectively. Chi square test was used. The correlation analysis was performed by Pearson correlation/Kendall's tau method for parametric and nonparametric variables respectively. Data analysis was performed with Statistical Package for Social Sciences version 17 for Windows (SPSS Inc., USA). $P < 0.05$ was considered as statistically significant.

Results

The participants recruited were in the age group of 40–60years (table 1). Mean age of the subjects was 49.96 ± 10.9. Subjects were divided in two groups- Group A (HbA1C < 7.0%) with 59 participants and Group B (HbA1C > 7.0%) with 46 and the mean value of HbA1c was 7.5 ± 2.3. Age and gender distribution of subjects are mentioned in table 1.

The mean values of total RBC, WBC, and platelets were higher in poorly controlled diabetic subjects (Group B) and there was a significant difference of MCV, MCH, and total WBC count (table 1). Association of hba1c with cardiovascular risk markers and hepatic enzymes shows that the mean values were higher in Group B except HDL and significant association was found with SBP, DBP, HsCRP, and GGT, ALP, TGL, LDL-C, and TC (table 2).

The Pearson correlation/Kendal tau method was used to find any significant relationship between hematological parameters and the cardiovascular risk markers and hepatic enzymes among the participants.

Table 1: Association of hematological parameters in with HbA1C.

Parameters	HbA1C (%)		
	Group A ≤ 7	Group B > 7	P value
Total RBC ($\times 10^6$ µl)	4.56 ± 0.55	4.67 ± 0.42	0.284
Hb (g/dL)	12.95 ± 1.94	12.80 ± 1.91	0.69
PCV (%)	41.02 ± 4.69	40.89 ± 4.81	0.889
MCV (fL)	91.20 ± 8.73	87.52 ± 6.00	0.016*
MCH (pq)	28.48 ± 3.46	27.27 ± 2.71	0.054*
MC HC (g/dL)	31.16 ± 1.76	31.09 ± 1.68	0.829
RDW-SD (fL)	48.41 ± 6.75	46.25 ± 4.20	0.06
WBC ($\times 10^3$ µl)	7.34 ± 1.65	8.26 ± 2.01	0.012*
Neutro (%)	57.69 ± 10.38	58.87 ± 8.15	0.527
Lympho (%)	32.51 ± 7.56	32.20 ± 7.60	0.834
NL ratio (%)	1.97 ± 0.97	2.02 ± 0.91	0.795
Monocytes (%)	3.98 ± 1.12	3.64 ± 0.76	0.08
Eosinophils (%)	4.67 ± 4.64	4.81 ± 4.78	0.959
Basophils (%)	0.19 ± 0.75	0.18 ± 0.09	0.634
Platelet count ($\times 10^3$ µl)	272.34 ± 65.29	295.52 ± 78.24	0.101
PLCR(%)	28.05 ± 7.82	29.32 ± 6.55	0.379
PCT (%)	0.28 ± 0.05	0.30 ± 0.07	0.112
PDW (fL)	11.96 ± 2.02	12.49 ± 2.44	0.23
MPV (fL)	10.42 ± 0.96	10.68 ± 1.08	0.23

(*p < 0.05)

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Table 2: Association of cardiovascular risk markers with HbA1C.

Parameters	HbA1C (%)		
	≤7	>7	p value
SBP (mmHg)	121.02 ± 10.1	130.52 ± 17.05	0.001**
DBP (mmHg)	81.63 ± 5.311	85.52 ± 7.133	0.002*
BMI (Kg/m²)	25.9 ± 4.26	26.6 ± 4.68	0.432
HsCRP (mg/dL)	4.21 ± 4.59	7.45 ± 2.95	0.000**
GGT (U/l)	26.90 ± 9.60	35.23 ± 11.47	0.000**
SGOT (U/l)	24.70 ± 7.57	24.86 ± 8.46	0.917
SGPT (U/l)	22.34 ± 8.47	23.98 ± 11.33	0.396
ALP (U/l)	100.12 ± 23.05	114.41 ± 28.02	0.005*
HDL-C (mg/dL)	43.54 ± 9.75	42.96 ± 8.65	0.749
TGL (mg/dL)	135.59 ± 83.20	199.70 ± 171.65	0.033*
LDL-C (mg/dL)	114.27 ± 32.47	126.91 ± 33.35	0.053*
CHO (mg/dL)	179.46 ± 38.93	199.67 ± 42.08	0.012*

*p < 0.05 ** p <0.001

Table 3: Association between hematological parameters and cardiovascular risk markers among the entire study population (n = 105).

	HbA1C(%)		BMI(Kg/m²)		SBP(mmHg)		DBP(mmHg)	
	R	p value	R	p value	R	p value	r	p value
Total RBC (×10⁶ µl)	0.171	0.081	0.292**	0.003*	0.120	0.223	0.171	0.082
Hb (g/dL)	0.026	0.792	0.233*	0.017*	0.182	0.063	0.203**	0.037*
PCV (%)	0.51	0.603	0.224*	0.021*	0.105	0.289	0.118	0.229
MCV (fL)	–0.206*	0.035*	–0.044	0.658	–0.014	0.884	–0.057	0.56
MCH (pq)	–0.149	0.128	0.005	0.963	0.134	0.171	0.108	0.271
MC HC (g/dL)	0.022	0.826	0.097	0.323	0.317**	0.001*	0.333**	0.001*
RDW-SD (fL)	–0.226*	0.02*	–0.135	0.168	–0.203*	0.038*	–0.243*	0.012*
WBC (×10³ µl)	0.231	0.018	0.148	0.132	0.034	0.733	0.031	0.755
Neutro (%)	0.007	0.946	–0.029	0.772	0.066	0.507	0.013	0.895
Lympho (%)	–0.023	0.817	0.149	0.13	–0.104	0.289	–0.081	0.41
NL ratio (%)	–0.013	0.846	–0.108	0.103	0.057	0.437	0.042	0.581
Monocytes (%)	–0.128	0.194	–0.087	0.376	0.009	0.923	–0.065	0.51
Eosinophils (%)	0.008	0.907	–0.046	0.487	0.033	0.658	0.105	0.17
Basophils (%)	–0.054	0.586	–0.089	0.365	–0.047	0.633	–0.067	0.496
Platelet count (×10³ µl)	0.033	0.737	–0.026	0.792	–0.07	0.478	–0.029	0.769
PDW(fL)	0.177	0.071	0.083	0.400	0.063	0.526	0.027	0.788
MPV(fL)	0.199*	0.042*	0.065	0.511	0.034	0.733	–0.019	0.848
PLCR(%)	0.160	0.103	0.038	0.698	0.036	0.712	–0.008	0.934
PCT (%)	0.35	0.726	–0.030	0.758	–0.128	0.194	–0.089	0.368

*p < 0.05, ** p < 0.001

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Discussion

In our study HbA1C shows significance and negative correlation with MCV and RDW (table 3) as shown in the study done by B.N.Alamri et al., [17]. Inflammation which influences erythropoiesis could be a causative factor. Sadeer G. Al-Kindi et al., explained the association of RDW in the diabetes population with diabetes-related complications such as MI, stroke, and CKD [18]. In this study it was also observed that Hba1c shows significant and positive correlation with MPV. Manoj Saluja et al., observed that the development of vascular complication resulted in higher MPV which shows the activity of platelets in subjects with poor glycemic status. Based on this they concluded that MPV can be used as simple measures to find the vascular events in diabetes [16].

BMI shows a weak positive correlation with hematological parameters like RBC count, hemoglobin, RDW and neutrophil. Abdominal fat accumulation and insulin resistance mediates the general association between BMI and hematological parameters [19]. In our study total RBC count, Hb, and PCV show significance and positive correlation with BMI (table 3). Subjects recruited in our study were non- obese, as they were in the study done by Belete Biadgo et al. High RBC, hemoglobin, and hematocrit in diabetes could contribute to identify insulin resistance in non-obese individuals [20].

A study done on RDW in cardio vascular diseases shows a strong positive correlation of RDW with blood pressure [21]. Similarly, in our study RBC indices such as MHC and RDW show significant and positive correlation with SBP and DBP. Hb was found to be significant and positively

Table 4: Association between hematological parameters and lipid profile among the entire study population (n = 105).

	HDL-C(mg/dL)		TGL(mg/dL)		LDL-C(mg/dL)		CHO(mg/dL)	
	r	p value	r	p value	r	p value	r	p value
Total RBC ($\times 10^6$ µl)	–0.206*	0.035*	0.019	0.78	0.226*	0.02*	0.19*	0.052*
Hb (g/dL)	–0.210*	0.032*	0.132*	0.048*	0.139	0.156	0.161	0.1
PCV (%)	–0.217*	0.026*	0.157*	0.018*	0.179	0.068	0.199*	0.042*
MCV (fL)	–0.100	0.308	–0.077	0.247	–0.076	0.44	–0.014	0.891
MCH (pq)	–0.058	0.559	0.031	0.646	–0.066	0.504	0.007	0.945
MC HC(g/dL)	–0.038	0.700	–0.033	0.626	–0.009	0.929	0.051	0.605
RDW-SD(fL)	–0.093	0.347	–0.118	0.076	–0.177	0.07	–0.122	0.214
WBC($\times 10^3$ µl)	0.102	0.300	0.026	0.696	0.075	0.449	0.092	0.35
Neutro (%)	–0.099	0.316	–0.061	0.359	–0.188*	0.055*	–0.174	0.075
Lympho (%)	0.081	0.411	0.072	0.280	0.216*	0.027*	0.231*	0.018*
NL ratio (%)	–0.056	0.406	–0.060	0.364	–0.19**	0.004*	–0.193**	0.004*
Monocytes (%)	–0.100	0.308	0.042	0.536	–0.103	0.296	–0.098	0.321
Eosinophils (%)	0.055	0.416	–0.026	0.698	–0.006	0.927	0.000	0.996
Basophils (%)	–0.169	0.085	–0.006	0.942	0.076	0.443	0.093	0.343
Platelet count ($\times 10^3$ µl)	0.131	0.185	0.084	0.208	0.15	0.126	0.234*	0.016*
PDW(fL)	–0.054	0.586	–0.009	0.890	0.003	0.977	–0.040	0.684
MPV(fL)	–0.090	0.362	–0.030	0.651	0.012	0.901	–0.056	0.572
PLCR(%)	0.121	0.217	–0.018	0.790	0.020	0.838	–0.044	0.657
PCT (%)	0.113	0.252	0.083	0.219	0.197*	0.044*	0.026**	0.007*

*$p < 0.05$, ** $p < 0.001$

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correlated with DBP (table 3). B O Gobel et al., explained a possible mechanism for increase in blood pressure due to increased Hb levels which could lead to increase in blood viscosity which, in turn, can worsen cardiovascular function [22].

Numerous studies have shown that a high level of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) and lower levels of high-density lipoprotein cholesterol (HDL-C) are associated with increased risk of CVD [23–26]. In this study we observed that HDL –C is significant and negatively correlated with RBC Count, HB and PCV. Previous studies have shown that a high erythrocyte count can potentially plays protective role in patients with coronary atherosclerosis [27].Whereas TGL shows significant and positive correlation with Hb and PCV, LDL-C and total CHO are significant and negatively correlated with neutrophil and NL ratio and positively correlated with RBC's and lymphocytes. Total CHO was found to be significant and positively correlated with lymphocytes, platelets, and PCT (table 4). Similar study showed that lymphocyte count was significantly associated with high LDL-C, high TG, and low HDL-C. A study conducted on Chinese population provided evidence that both, the neutrophil count and the global registry of acute coronary events risk score, are independent and joint predictors for major adverse cardiovascular events [29]. Total CHO and TG levels were also consistently and positively associated with total leukocyte, neutrophil, and lymphocyte counts [29]. Modulation of platelet activity in platelets biogenesis takes place in hypercholestremia [30]. In our study we also found that WBC, RBC, platelets, and its indices showed significance with different lipid parameters.

In our study HsCRP, a prime systemic inflammatory marker, shows strong significance and positive correlation with total WBC, neutrophil, and platelet indices such as MPV, PLCR and PCT, whereas it shows significance and negative correlation with RDW, lymphocytes, NL ratio, and monocytes (table 5). Similarly, several studies have reported a relationship between various markers of inflammation and blood cell indices. A correlation between serum levels of CRP and RDW has been described in patients with hypertension, coronary artery disease, Alzheimer's disease and in overweight adolescents [31–35]. Studies have shown that hsCRP, as well as WBC count, high neutrophils levels and low lymphocytes levels, can independently predict vascular risk in apparently both healthy men and women and also in patients with signs of CVD [36–39].

In our finding we found positive correlation of HsCRP with PCT, MPV, and PLCR. Mean platelet volume (MPV) is a major determinant of platelet functionality and higher MPV is related with a risk of cardiovascular disease like stroke, myocardial infarction, and transient ischemic attacks [40]. Similar to our study, Farah Jabeen et al., show a positive association of platelet indices with HsCRP in T2DM and also concluded that platelet indices are vital markers in early detection of diabetic complications [41].

Of all hepatic enzymes, GGT has emerged as a biomarker of cardiovascular diseases [9] Christian Obirikorang et al showed that GGT has accuracy in predicting the risk of cardiovascular diseases among diabetes mellitus individuals [43]. Previous studies demonstrated the relation between GGT and cardio vascular diseases such as hypertension, arterial stiffness, coronary artery diseases, heart failure, and pulmonary embolism [44–48]. In our study GGT are significant and positively correlated with RBC's and its indices. AST, ALT and ALP also show significance and correlation with different blood parameters. Vipin Goyal et al., explained that RBC count, HGB, and WBC count and concentration, were all higher in FLD group with increased GGT, ALP and AST. Possible mechanism could be that the oxidative stress might enhance compensatory erythropoiesis in chronic inflammatory diseases, such as atherosclerosis, coronary artery disease, metabolic syndrome, and FLD. The main physiological roles of RBCs are not only transporting oxygen and carbon dioxide but also scavenging reactive oxygen and nitrogen species. As FLD is frequently accompanied with inflammation and oxidative damage, RBC indices have been suggested to be associated with inflammatory markers, generation of RBCs may be increased. Also the capacity of spleen and liver for scavenging RBCs might be damaged

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Table 5: Association between the hematological parameters with inflammatory. Marker and hepatic enzymes among the entire study population (n = 105).

	HsCRP(%)		GGT(U/l)		AST(U/l)		ALT(U/l)		ALP(U/l)	
	R	p value	R	p value	R	p value	r	p value	r	p value
Total RBC (×10⁶ µl)	0.182	0.064	0.281**	0.004*	0.058	0.557	0.295**	0.002*	0.105	0.288
Hb (g/dL)	–0.111	0.259	0.387**	0.000	0.286**	0.003*	0.459**	0.000	–0.017	0.861
PCV (%)	–0.069	0.484	0.388**	0.000*	0.218*	0.025*	0.414**	0.000	0.006	0.951
MCV (fL)	–0.391*	0.000*	0.172	0.08*	0.23*	0.018*	0.202*	0.039*	–0.154	0.117
MCH (pq)	–0.329**	0.001	0.238*	0.015*	0.338**	0.000*	0.322**	0.001*	–0.110	0.265
MC HC (g/dL)	–0.084	0.395	0.248*	0.011*	0.346**	0.000*	0.369**	0.000*	0.023	0.814
RDW-SD (fL)	–0.196*	0.045*	–0.065	0.507	0.108	0.272	–0.074	0.455	–0.189	0.053
WBC (×10³ ML)	0.365**	0.000*	0.15	0.126	–0.106	0.283	–0.046	0.643	0.28**	0.004*
Neutro (%)	0.294**	0.002*	–0.083	0.398	–0.053	0.591	–0.115	0.244	0.074	0.451
Lympho (%)	–0.259**	0.008*	0.139	0.157	0.107	0.279	0.199*	0.042*	–0.086	0.384
NL ratio (%)	–0.189**	0.005*	–0.103	0.119	–0.180**	0.007*	–0.166*	0.012	0.023	0.723
Monocytes (%)	–0.206*	0.035*	–0.028	0.779	0.129	0.19	0.111	0.262	–0.103	0.297
Eosinophils (%)	–0.019	0.775	–0.055	0.406	–0.035	0.597	–0.093	0.162	0.082	0.216
Basophils (%)	–0.157	0.11	0.043	0.666	0.094	0.342	0.008	0.932	–0.078	0.431
Platelet count (×10³ µl)	0.168	0.088	–0.010	0.917	–0.189	0.053	–0.192*	0.050*	–0.144	0.142
PDW(fL)	0.11	0.910	0.037	0.706	–0.120	0.223	–0.077	0.435	–0.043	0.660
MPV(fL)	–0.005	0.957	0.049	0.618	–0.079	0.423	–0.044	0.656	–0.039	0.693
PLCR (%)	0.067	0.500	0.048	0.628	–0.078	0.426	–0.045	0.646	–0.059	0.552
PCT (%)	0.154	0.116	0.026	0.769	–0.211*	0.031*	–0.187	0.057	0.105	0.285

*p < 0.05, ** p < 0.001

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in FLD condition, leading to further increase of RBC count [49, 50].

Conclusion

Even though HsCRP and hepatic enzymes are known to be effective biomarkers for evaluating risk of cardio vascular diseases in T2DM patients, from our study it is concluded that hematological parameters such as Total RBC, WBC, platelet count along with its indices can also be used for assessing risk factors of cardio vascular diseases. Periodic estimation of HbA1C with Complete Blood Count profile in T2DM patients will help in the early detection of inflammatory changes and prognosis of Cardio vascular diseases.

Conflict of Interest

The authors declare no conflict of interest.

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Original Research

1-Hour post-load glycemic value in risk population: a better tool for type 2 diabetes screening?

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Abstract

Background and Aims: Type 2 diabetes mellitus (T2DM) is a chronic disease with a negative impact by decreasing the life quality and expectancy of patients. The PREDATORR study, which started in 2013 in our country showed double prevalence to previous data. In 2000, the World Health Organization drew attention to the fact that it is the first time that a non-infectious disease has become epidemic, replacing the major health problems of the last century. The study evaluates the usefulness of measuring one hour post-load blood glucose during an oral glucose tolerance test in T2DM risk population. **Material and Method:** The subjects included in the study were selected over a period of two years from the patients' families of the Diabetes, Nutrition, and Metabolic Diseases Outpatient Unit of the "St. Andrew" Emergency Clinical County Hospital of Constanta. The assessment was made based on the risk score for diabetes (FIND RISC), anthropometric indices, and glucose metabolism parameters. The statistical analysis was performed in SPSS 27.0, STATA and Microsoft Excel. **Results:** The studied population consisted of 112 subjects, 38.4% being included in the control group and 61.6% in the study group. In the analysis of risk factors present in the study group, pre-diabetes was identified in 36.2% of patients, exclusively characterized by impaired fasting glucose. The values of FIND RISC score were much higher in the study group than in the control group. The BMI was higher in the study group compared to the control group. In 65.8% of patients regarding basal glycemia and 80% regarding glycated hemoglobin, the values did not exceed the pathological threshold. In the study group, 1-hour post-load blood glucose identified more patients at risk for T2DM than 2-hour post-load glycemic value. **Conclusions:** Evaluation of glucose metabolism parameters through the oral glucose tolerance test may be useful in screening for T2DM and the measurement of 1-hour post-load blood glucose can be used successfully among patients at risk.

Keywords: screening, type 2 diabetes, 1-hour post-load glycemia.

Background and Aims

Type 2 diabetes mellitus (T2DM) is defined by chronic hyperglycemia in the background of insulin deficiency itself or associated insulin resistance with negative effect on carbohydrate, protein, and lipid metabolism [1].

In recent years, many studies identified various clinical conditions associated with insulin resistance and compensatory hyperinsulinemia such as pre-diabetes, metabolic syndrome, obesity, dyslipidemia, primary arterial hypertension, polycystic ovary syndrome, atherosclerosis, hepatic steatosis or even the family history of T2DM [2].

Over time, International Diabetes Federation (IDF) tried to draw attention to the potential burden of diabetes, but even their prediction did not estimate the real impact. Nowadays, there is a dramatic trend of diabetes globalization in the background of obesity, another worldwide health problem [3, 4]. The major environmental changes after 2nd World War were directly involved in creating an obesogenic environment through poor

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quality food supply and decrease of daily physical activity [5].

In 2019, IDF declared 463 million patients diagnosed with diabetes and estimated for 2045 an increase of 51% [6]. The recent study conducted in our country, PREDATORR, showed doubled prevalence of 11.6% compared to previous local data [7, 8].

In 2000, the World Health Organization drew attention to the fact that it is the first time that a non-infectious disease has become epidemic, replacing the major health problems of the last century.

T2DM is a chronic disease with a negative impact by decreasing the life quality and expectancy of patients [9, 10].

The study evaluates the usefulness of measuring one-hour post-load blood glucose during a oral glucose tolerance test in T2DM risk population.

Material and Method

Being a case control study, it consisted of two groups selected over a period of two years from the family patients of the Diabetes, Nutrition and Metabolic Diseases Outpatient Unit of the "St. Andrew" Emergency Clinical County Hospital of Constanta. The inclusion and exclusion criteria are presented in table 1.

Table 1: Inclusion and exclusion criteria for the studied groups.

	Study group	**Control group**
Inclusion criteria	✓ Age between 18–75 years old; ✓ Romanian ethnicity; ✓ risk groups association: • Family history of T2DM; • Personal history of prediabetes (impaired fasting glucose - IFG and/ or impaired glucose tolerance - IGT); • Overweight or obesity; • Gestational diabetes (GD); • Polycystic ovary syndrome (PCOS); • Arterial hypertension/ Myocardial infarction; • dyslipidemia; • hepatic steatosis;	✓ Age between 18–75 years old; ✓ Romanian ethnicity; ✓ BMI <25 kg/m^2);
Exclusion criteria	✓ Age under 18 years or over 75 years old; ✓ Personal diagnosis of T2DM; ✓ BMI<25 kg/M^2; ✓ Women during pregnancy or breastfeeding period; ✓ Recent surgical procedures; ✓ Other known chronic diseases (chronic pancreatitis, chronic hepatitis, liver cirrhosis, cancers, hemochromatosis, HIV infection); ✓ Chronic consumption of alcohol (>40 g/ daily on men and 20 g/daily on woman).	✓ Age under 18 years or over 75 years old; ✓ Personal diagnosis of T2DM; ✓ risk groups association: • Family history of T2DM; • Personal history of prediabetes (IFG glucose and/or IGT); • Overweight or obesity; • GD; • PCOS; • Arterial hypertension/ myocardial infarction; • dyslipidemia; • hepatic steatosis; ✓ Women during pregnancy or breastfeeding period; ✓ Recent surgical procedures; ✓ Other known chronic diseases (chronic pancreatitis, chronic hepatitis, liver cirrhosis, cancers, hemochromatosis, HIV infection); ✓ Chronic consumption of alcohol (>40 g/ daily on men and 20 g/daily on woman).

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After inclusion in the study, the subjects of both groups were evaluated taking into account demographic data, family and personal pathological history, FIND RISC diabetes risk score, anthropometric indices (weight, height, BMI) and glucose metabolism parameters (fasting glycemia, 1-hour post-load and 2-hour post-load glycemia measured during the oral glucose tolerance test, glycated hemoglobin, after a nocturnal fasting for at least 8 hours, respectively after ingestion of 75 g of glucose dissolved in 200 ml of water). The statistical analysis was performed in SPSS 27.0, STATA and Microsoft Excel.

Results

The studied population consisted of 112 patients, divided in two groups: the control group, represented by 43 subjects (38.4%) and the study group consisting of 69 patients with risk for T2DM (61.6%). There is a balanced gender distribution (table 2), the investigated subjects belonging to adulthood with a mean value of 44.25 ± 13,348 years (table 3).

In the study group, T2DM was reported in first and second-degree relatives in 31.9% of cases. Those who had a history of first-degree relatives, accounted for 23.2%. A history of T2DM only to second degree relatives has been identified in 14.5% of patients. (table 4).

Following the risk factors analysis in the study group, pre-diabetes was the most frequently identified (36.2%), characterized exclusively by impaired fasting glucose (table 5).

We have counted the FIND RISC score for both groups, and we have identified that its values are much higher in the study group (13.90 ± 5,145) compared to the control group (5.35 ± 2,608), the differences being statistically significant (table 6). All patients of the control group had a low to moderate FIND score. In the study group, low to moderate risk was present in 58% of subjects, while the remaining 42% were at high and very high risk. One third of patients (31.9%) had a high FIND score and 10.1% had a very high FIND score (table 7). The patients' risk of diabetes varies in the same way: in 74.1% of patients (control group) and 58.0% of the others (study group), the risk is between 1–17%, meanwhile in 31.9% of patients of the control group there is a 33% risk of diabetes and in 10.1% of the same ones there is a 50% risk of diabetes (table 7).

We measured the anthropometric parameters (weight, height) and counted the body mass index (BMI) to identify the presence or absence of obesity. The recorded values are presented in detail, compared by gender and groups in table 8. In the control group, there were no overweight or obese patients, over 90% of them having BMI <25 kg/m^2. In the study group, the percentage of patients with normal weight decreased

Table 2: Gender distribution of both groups.

		Group						Pearson Chi-square	P
		Study		Control		Total			
		n	%	n	%	n	%		
Gender	Male	28	40.6%	17	39.5%	45	40.2%		
	Female	41	59.4%	26	60.5%	67	59.8%		
Total		69	100.0%	43	100.0%	112	100.0%	.012	.913

Table 3: Age - descriptive statistic parameters of both groups.

Group	N	Mean	Standard error	Standard deviation	Minimum	Maximum
Study	69	42.86	1.652	13.724	27	74
Control	43	46.49	1.914	12.553	25	61
Total	112	44.25	1.261	13.348	25	74

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Table 4: Distribution according to family history of the study group.

Family history	Group				Total		Pearson Chi-square	p
	Study		Control					
	n	%	n	%	n	%		
without	21	30.4%	43	100.0%	64	57.1%		
1st degree	16	23.2%			16	14.3%	35.842	.000*
2nd degree	10	14.5%			10	8.9%	27.919	.000*
1st and 2nd degree	22	31.9%			22	19.6%		
Total	69	100.0%	43	100.0%	112	100.0%	52.348	.000*

Table 5: Distribution of other T2DM risk factors of the study group.

		Group				Total		Pearson Chi-square	p
		Study		Control					
		n	%	n	%	n	%		
Prediabetes	yes	25	36.2%	0	0.0%	25	22.3%	20.057	.000*
	no	44	63.8%	43	100.0%	87	77.7%		
IFG	yes	25	36.2%	0	0.0%	25	22.3%	20.057	.000*
	no	44	63.8%	43	100.0%	87	77.7%		
IGT	yes	0	0.0%	0	0.0%	0	0.0%	–	–
	no	69	100.0%	43	100.0%	112	100.0%		
GD	yes	10	24.4%	0	0.0%	10	14.9%	7.454	.006*
	no	31	75.6%	26	100.0%	57	85.1%		
Dyslipidemia	yes	10	14.5%	0	0.0%	10	8.9%	6.843	.007*
	no	59	85.5%	43	100.0%	102	91.1%		
Arterial hypertension	yes	17	24.6%	0	0.0%	17	15.2%	12.490	.000*
	no	52	75.4%	43	100.0%	95	84.8%		
Myocardial Infarction	yes	2	2.9%	0	0.0%	2	1.8%	1.269	.523
	no	67	97.1%	43	100.0%	110	98.2%		
Hepatic Steatosis	yes	7	10.1%	0	0.0%	7	6.3%	4.653	.042*
	no	62	89.9%	43	100.0%	105	93.8%		
PCOS	yes	6	14.6%	3	11.5%	9	13.4%	.131	1.000
	no	35	85.4%	23	88.5%	58	86.6%		
Total		69	100.0%	43	100.0%	112	100.0%		

significantly (26.1%), most of them being overweight (21.7%), 1st stage obesity (31.9%) or even with 2nd stage obesity (14.5%) (table 9, figure 1).

We also analyzed the glucose metabolism parameters by determining fasting glucose (FG), 1-hour (1-hG) and 2-hour (2-hG) post-load glycemic value during the oral glucose tolerance test (OGTT) and glycated hemoglobin (HbA1c).

The mean value of fasting glucose was higher in the study group (93.91 ± 14,961) compared to the control group (89.21 ± 5,734) (table 10). All patients in the control group had

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Table 6: FIND score - descriptive statistic parameters in both groups.

Group	N	Mean	Standard error	Standard deviation	Minimum	Maximum
Study	69	13.90	.619	5.145	5	25
Control	43	5.35	.398	2.608	0	8
Total	112	10.62	.569	6.020	0	25

Table 7: Category distribution of the FIND RISC score in both groups.

Risk category – FIND score	Group						Pearson Chi-square	p
	Study		Control		Total			
	n	%	n	%	n	%		
Low to moderate	40	58.0%	43	100.0%	83	74.1%		
High	22	31.9%	0	0.0%	22	19.6%		
Very high	7	10.1%	0	0.0%	7	6.3%		
Total	69	100.0%	43	100.0%	112	100.0%	24.387	.000*

Table 8: BMI - descriptive statistic parameters, comparative by gender, in both groups.

Group	Gender	N	Mean	Standard error	Standard deviation	Minimum	Maximum
Study	Male	28	30.8746	.50654	2.68037	25.64	35.06
	Female	41	25.8551	.91248	5.84271	18.14	36.92
	Total	69	27.8920	.64939	5.39426	18.14	36.92
Control	Male	17	23.6412	.26378	1.08761	22.09	24.87
	Female	26	22.1481	.42841	2.18449	17.83	24.34
	Total	43	22.7384	.29871	1.95875	17.83	24.87
Total	Male	45	28.1420	.62214	4.17342	22.09	35.06
	Female	67	24.4166	.62066	5.08031	17.83	36.92
	Total	112	25.9134	.47824	5.06126	17.83	36.92

Table 9: Obesity distribution in both groups (according to BMI).

BMI category	Group						Pearson Chi-square	P
	Study		Control		Total			
	n	%	n	%	n	%		
underweight	4	5.8%	3	7.0%	7	6.3%		
normal weight	18	26.1%	40	93.0%	58	51.8%		
overweight	15	21.7%	0	0.0%	15	13.4%		
1st stage obesity	22	31.9%	0	0.0%	22	19.6%		
2nd stage obesity	10	14.5%	0	0.0%	10	8.9%		
Total	69	100.0%	43	100.0%	112	100.0%	52.269	.000*

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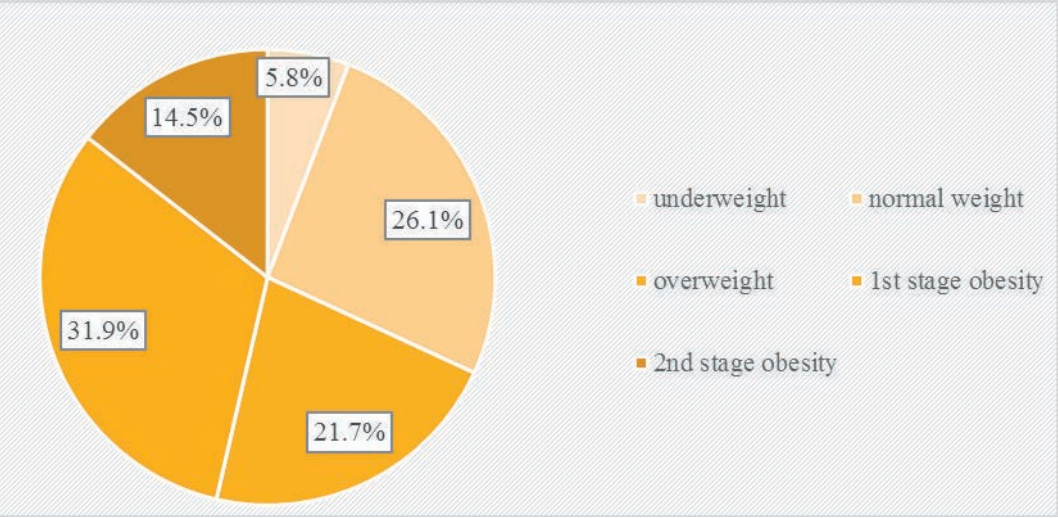

Figure 1: Weight category distribution in the study group (according to BMI).

Table 10: Fasting glycemia - descriptive statistic parameters in both groups.

Group	N	Mean	Standard error	Standard deviation	Minimum	Maximum
Study	69	93.91	1.801	14.961	74	134
Control	43	89.21	.874	5.734	78	99
Total	112	92.11	1.176	12.444	74	134

normal blood glucose values. In the study group, normal values of this parameter were recorded only in 65.2% of patients, 26.1% being with impaired fasting glucose and 8.7% with baseline values for T2DM. Consequently, the differences between the two groups are statistically significant (table 11, figure 2).

The mean value of 1-hour post-load glycemia was higher in the study group (156.39 ± 47,862) compared to the control group (126.51 ± 37,095), the differences being statistically significant (table 12). In the control group, over 80% of patients had values below 155 mg/dl. In the study group, 43.5% had 1-hG less than 155 mg/dl, 31.9% had a value between 155 and 200 mg/dl and 24.6% with a value over 200 mg/dl (table 13, figure.3).

The 2-hour post-load blood glucose (2-hG) had a higher mean value in the study group (116.42 ± 38,706) compared to the control group (98.16 ± 15,964) (table 14). All patients in the control group had normal values (NGT) for 2-hG, while in the study group the percentage of patients with NGT was reduced to 81.2%, impaired glucose tolerance (IGT) being identified in 15.9% of cases and T2DM in 2.9% of patients (table 15, figure 4).

The mean value of glycosylated hemoglobin (HbA1c) was higher in the study group

Table 11: Fasting glycemia - categories distribution of both groups.

FG	Group				Total		Pearson Chi-square	P
	Study		Control					
	n	%	n	%	n	%		
Normal	45	65.2%	43	100.0%	88	78.6%		
IFG	18	26.1%	0	0.0%	18	16.1%		
T2DM	6	8.7%	0	0.0%	6	5.4%		
Total	69	100.0%	43	100.0%	112	100.0%	19.036	.000*

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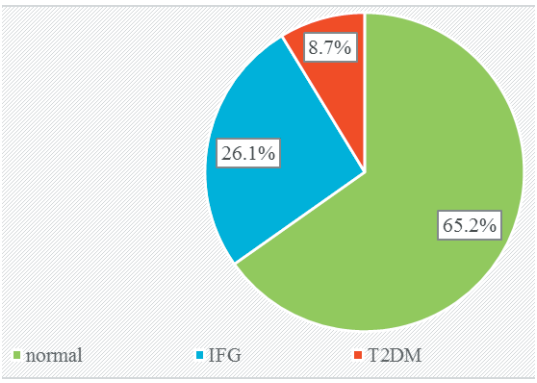

Figure 2: Fasting glycemia - categories distribution of the study group.

(5.44493 ± 0.334108) compared to the control group (5.39302 ± 0.222961), this time without statistically significant differences between groups (table 16). Over 80% had normal values for this parameter, pre-diabetes being thus identified only in 18.8% of them (table 17, figure 5). This suggests that HbA1c was not effective in identifying all patients at risk for diabetes.

We used the receiver operating characteristic (ROC) analysis and area under the curve (AUC) to identify the cutt-off values of blood tests used for diabetes predisposition, respectively the

Table 12: 1-hour post-load glycemia - descriptive statistic parameters in both groups.

Group	N	Mean	Standard error	Standard deviation	Minimum	Maximum
Study	69	156.39	5.762	47.862	62	253
Control	43	126.51	5.657	37.095	68	205
Total	112	144.92	4.368	46.229	62	253

Table 13: 1-hour post-load glycemia - categories distribution of both groups.

1 hG	Group						Pearson Chi-square	P
	Study		Control		Total			
	n	%	n	%	n	%		
<155 mg/dl	30	43.5%	36	83.7%	66	58.9%		
155–200 mg/dl	22	31.9%	3	7.0%	25	22.3%		
200 mg/dl	17	24.6%	4	9.3%	21	18.8%		
Total	69	100.0%	43	100.0%	112	100.0%	17.966	.000*

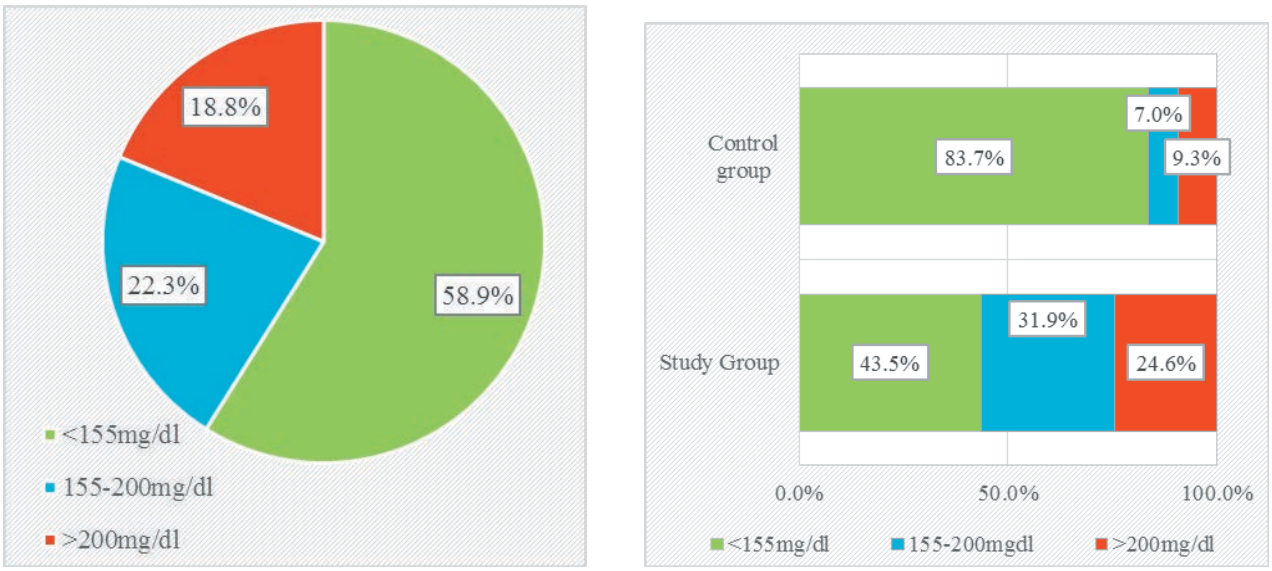

Figure 3: 1-hour post-load glycemia – categories distribution of both groups.

Table 14: 2-hour post-load glycemia - descriptive statistic parameters in both groups.

Group	N	Mean	Standard Error	Standard Deviation	Minimum	Maximum
Study	69	116.42	4.660	38.706	61	247
Control	43	98.16	2.435	15.964	68	117
Total	112	109.41	3.125	33.072	61	247

Table 15: 2-hour post-load glycemia - categories distribution of both groups.

2hG	Group						Pearson Chi-square	p
	Study		Control		Total			
	n	%	n	%	n	%		
NGT	56	81.2%	43	100.0%	99	88.4%		
IGT	11	15.9%	0	0.0%	11	9.8%		
T2DM	2	2.9%	0	0.0%	2	1.8%		
Total	69	100.0%	43	100.0%	112	100.0%	9.165	.010*

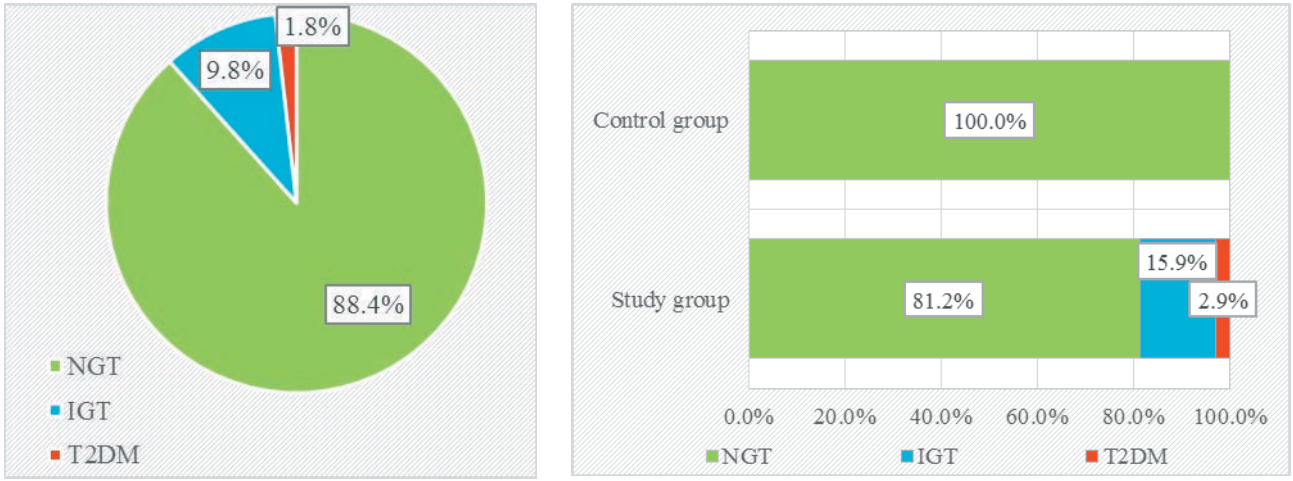

Figure 4: 2-hour post-load glycemia – categories distribution of both groups.

patients' affiliation to the study group compared to the control group. To choose the appropriate cut-off value, we took into consideration the sensitivity, specificity, and maximum of these two (Youden's coefficient). The obtained results are presented in table 18..

We noticed that both fasting glycemia and HbA1c did not identify all patients with risk factors for diabetes, much more useful being the 1-hour post-load and 2-hour post-load glycemic values. Statistical analysis showed that 1-hG is more predictive with a cutt-off value of 142.5 (table 18, figure 6) in comparison with the value of 155 mg/dl mentioned in the literature [11].

Discussions

From the T2DM family history point of view, there are statistically significant differences between the two investigated groups, which showed that its presence can be systematically associated with the risk of diabetes, a fact also stated by the literature data.

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Table 16: HbA1c - descriptive statistic parameters in both groups.

Group	N	Mean	Standard Error	Standard Deviation	Minimum	Maximum
Study	69	5.44493	.040222	.334108	4.700	6.000
Control	43	5.39302	.034001	.222962	4.900	5.800
Total	112	5.42500	.028005	.296374	4.700	6.000

Table 17: HbA1c - categories distribution of both groups.

HbA1c	Group						Pearson Chi-square	p
	Study		Control		Total			
	n	%	n	%	n	%		
Normal	54	78.3%	37	86.0%	91	81.3%		
Prediabetes	15	21.7%	6	14.0%	21	18.8%		
Total	69	100.0%	43	100.0%	112	100.0%	1.054	.305

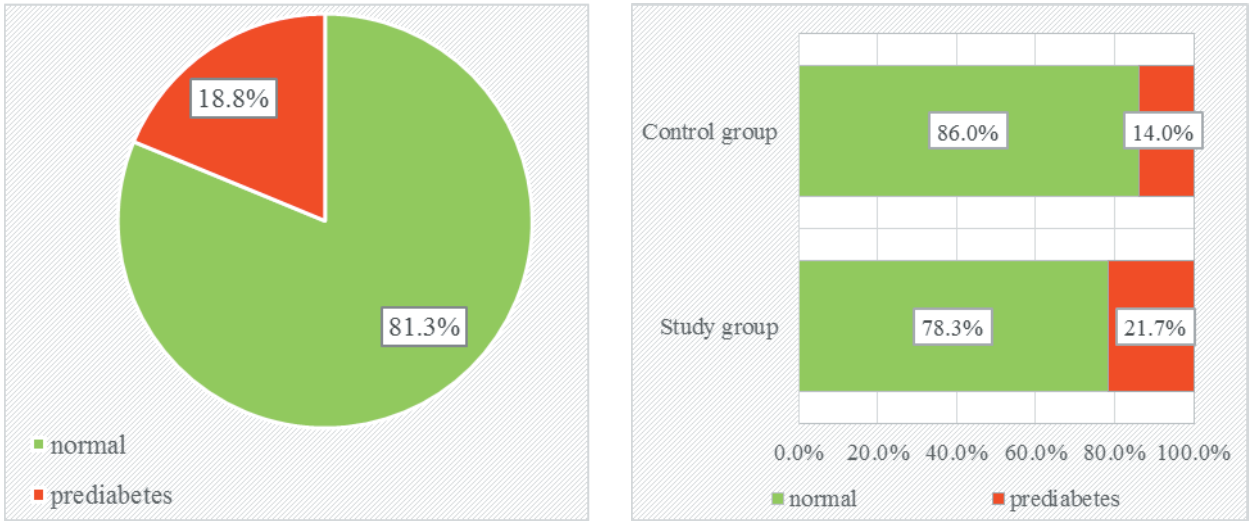

Figure 5: HbA1c - categories distribution of both groups.

Table 18: ROC analysis for blood glucose and HbA1c.

	AUC	p	95% AUC Confidence Interval		Cut-off Value	Sensitivity	Specificity
			Inf.L.	Sup.L.			
FG	.559	.291	.454	.665			
1-hG	.682	.001*	.582	.782	142.5	0.652	0.767
2-hG	.643	.011*	.541	.745	109.0	0.565	0.837
HbA1c	.538	.495	.432	.645			

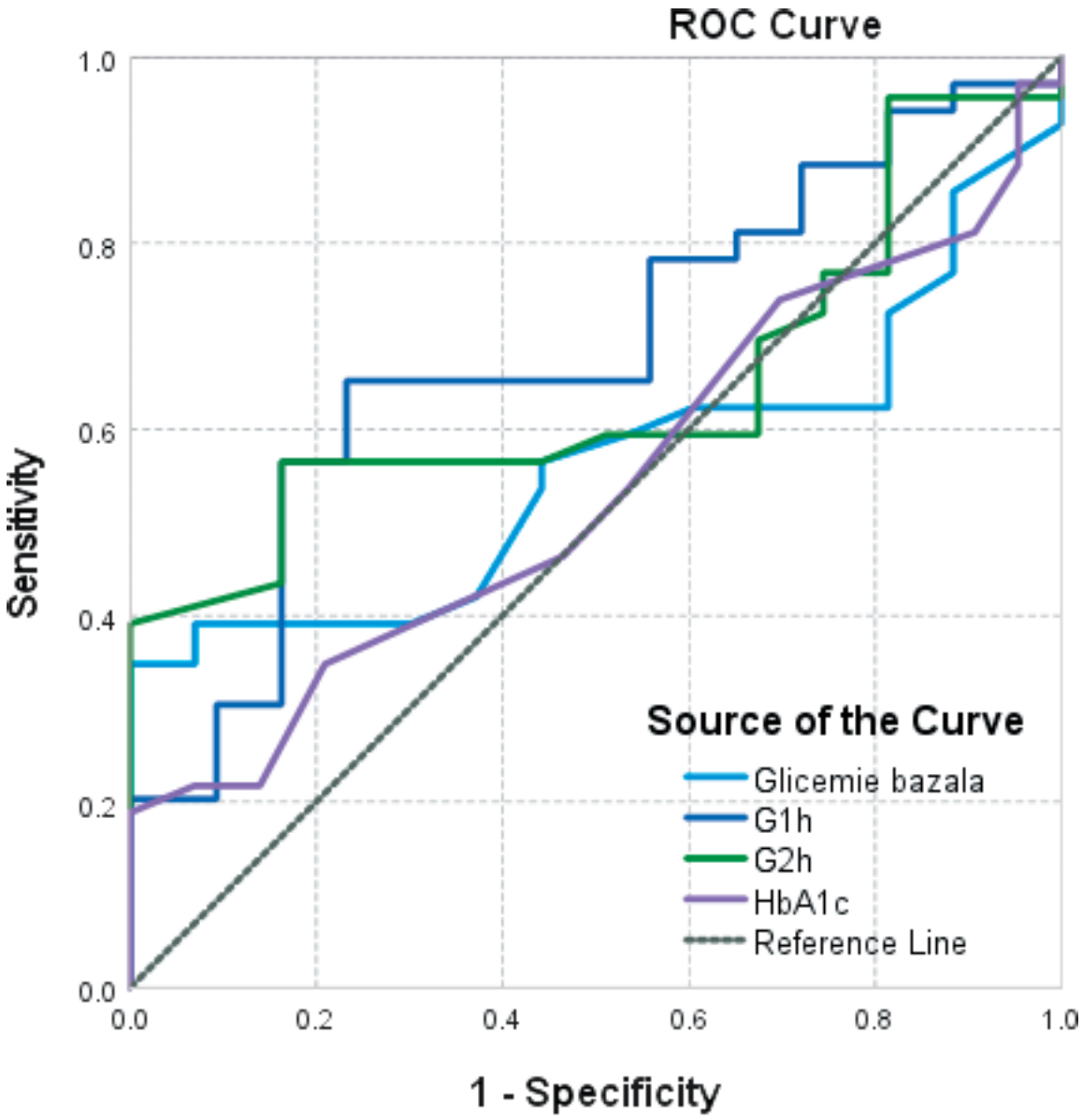

Figure 6: ROC curves for blood glucose and HbA1c.

The FIND RISC score proves once again its usefulness in assessing the risk of diabetes as showed in many studies [12, 13].

Overweight and obesity were identified in the study group in a percentage similar to the one reported in the PREDATORR study (>60%) [8].

Fasting glycemia and HbA1c have not been effective in identifying patients at risk, the 1-hour post-load and 2-hour post-load glycemia measured during 75 g OGTT being more useful in this regard.

Recent studies suggested that a 1-hG cut off value above 155 mg/dl represents a risk for developing T2DM and places it as an intermediate risk category between impaired fasting glucose and impaired glucose tolerance [11, 14]. Hisayama Study suggested that a 30 min post-load glycemia is also helpful to predict T2DM and stated a cut off value of 173mg/dl for detecting the high-risk population [15].

In our study, it seems that 1-hour post-load plasma glucose is more accurate in assessing the risk of diabetes, 50% of patients having a value above 155 mg/dl. 1-hG demonstrated its superiority also by identifying its risk values in over 50% of patients in the study group, 2-hG achieving this in only 30% of cases for a risk value above 140 mg/dl.

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Furthermore, a prospective population-based cohort study suggested that 1-hG gives us information regarding the risk for diabetes complications [11]. Recent evidence showed similar ability between 1-h and 2-h post-load glucose level to predict diabetic retinopathy [16]. However, it seems that 1-h post-load glycemia is an independent risk factor for cardiovascular disease also [17].

Long term studies on larger populations will better confirm our results regarding 1-hour post-load glycemic value being a better tool for type 2 diabetes screening.

Conclusion

Evaluation of glucose metabolism parameters through the 75 g oral glucose tolerance test may be useful in screening the type 2 diabetes risk population, evaluation of 1-hour post-load glycemia being more predictive for diagnosis.

Conflict of Interest

The authors declare no conflict of interest.

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Original Research

Nutritional label use among patients with type 1 diabetes mellitus

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Abstract

Background and Aims: In this study, it was aimed to evaluate the nutritional label use of individuals with type 1 DM. **Material and Method:** This cross-sectional descriptive study was conducted in November 2017 - June 2018. Diabetic individuals were reached through hospitals and social networks. The study was conducted with 105 (64 female, 41 male) individuals with type 1 DM living in Istanbul. A questionnaire about sociodemographic characteristics, biochemical parameters, medical treatment, food label reading status, food label reading reasons were applied in the study. Data were analyzed using SPSS V 16.0 program. **Results:** 85.7% of the participants read the food label. No significant difference was found when age group and nutritional label reading status were examined ($p > 0.05$). Besides, information was given to 67.6% of the participants about reading the nutritional label. A significant association was found between nutritional label reading knowledge and carbohydrate counting application and stages ($P=0.0001$). However, there was no significant difference between biochemical parameters and reading label status ($p>0.05$). **Conclusions:** Nutritional label reading should be mentioned more in the medical nutrition therapy and diabetes education.

Keywords: Type 1 diabetes, nutritional label, carbohydrate counting, diabetes education.

Background and Aims

Diabetes mellitus (DM) is a chronic and metabolic disease in which the organism cannot use carbohydrates, fats, and proteins sufficiently due to insulin deficiency or insulin-effect defects, requiring constant medical care [1]. Type 1 diabetes is a type of diabetes caused by an autoimmune reaction in which the body's immune system attacks beta cells of insulin-producing pancreatic islets [2]. A total of 1 106 200 children under the age of 20 and adolescents worldwide are thought to have Type 1 diabetes. Type 1 diabetes accounts for more than 90% of childhood and adolescent diabetes in most western countries, while it accounts for 5-10% of people with diabetes in the entire population. According to the results of the first nationwide study to determine the incidence and prevalence of diabetes in Turkey, the number of Type 1 diabetes under the age of 18 have been found to be 17 175. According to these results, Type 1 diabetes cases in Turkey constitute approximately 3% of Type 1 diabetes cases of the World [3,4].

In the treatment of diabetes, one has to be able to manage his or her lifestyle, and insulin, medical nutrition therapy, and exercise are the mainstays of treatment. Nutritional management of people with diabetes can be achieved by choosing healthy food, providing portion control, reading and understanding nutritional

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labels, counting carbohydrates, and eating at the right time [5,6].

One of the most challenging and ambitious goals that public health is trying to achieve worldwide is to promote healthy living and nutrition. Nutritional related health problems such as obesity, diabetes, and metabolic syndrome have a significant impact on societies. In order to enable individuals to make safer and more conscious choices about their health, the entire population should be encouraged to use the nutritional label effectively [7].

Carbohydrate counting, which is recommended to provide better glycemic control to patients with diabetes, is a meal planning method that allows the adjustment of the amount of carbohydrate to be consumed in the meals and also provides the adjustment of the insulin dose required by the individual according to the pre-meal blood glucose. Carbohydrate counting method requires the ability to read the nutritional labels [1,8].

Nutritional labels are the materials by which the percentage of the nutrients (protein, fat, vitamins, minerals, etc.) of packaged foods and how much of the nutrients the consumer needs to receive daily [9]. According to Turkish Food Codex Regulation on Food Labeling and Informing Consumers, the label refers to any mark, brand, stamp, pictorial or other identifying element printed on the packaging or container of food, printed, stencil-printed, marked, embossed, cold-printed, glued, or affixed [10].

Nutritional label reading is known to facilitate carbohydrate counting and provide glycemic control. In addition, it has been shown that nutritional knowledge has a role in weight control and healthy nutrition and shortening duration of diabetes [11]. Therefore, health and number literacy are essential for understanding healthy nutrition, which plays an important role in the prevention and management of diabetes [6,12]. However, little is known about the prevalence of the use of nutritional labels in the type 1 diabetic population [13].

The aim of this study was to evaluate the nutritional label use, and the reasons affecting label reading status of patients with type 1 diabetes mellitus. The second aim was to determine the effect of label reading information on the attitude of the type 1 diabetes mellitus patients.

Material and Method

Study design and patients

This cross-sectional descriptive study was conducted in November 2017 - June 2018 with 105 individuals aged between 10-30 years with type 1 diabetes mellitus living in Istanbul. Diabetic individuals were reached through hospitals and social networks. Necessary permissions were obtained from hospitals. Permission of the Ethics Committee No. 09.2017.657 was obtained from the Marmara University Faculty of Medicine Clinical Research Ethics Committee. Before the study, participants were informed about the study and their consent was obtained. The families of children and adolescents were also informed and their consent was obtained.

Laboratory, anthropometric and clinical data collection

The study was conducted by face to face interview method. In the first part of the questionnaire, information on gender, age, occupation, education level, and income level was obtained. The questionnaire also included questions about diabetes duration, fasting plasma glucose (FPG), HbA1c values in the last three months and frequency of hypoglycemia.

Fasting plasma glucose and HbA1c values of children were evaluated using International Society for Pediatric and Adolescent Diabetes (ISPAD) data, according to Diabetes Control and Complications Trial (DCCT) standard and Turkey Endocrinology and Metabolism Association (TEMD) recommendations, whereas the evaluation of FPG and HbA1c values of adults was conducted according to the TEMD recommendations [1,14]:

- For 8-12 years; FPG 90-180 mg/dl, HbA1c <%8,0
- For 13-18 years; FPG 80-120 mg/dl, HbA1c %6,5-7
- For >18 years; FPG 80-130 mg/dl, HbA1c <%7 were considered good glycemic control.

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Information on the anthropometric measurements of the participants was obtained from questions regarding the height, body weight, and body mass index (BMI) of the participants. Body mass indices of individuals with diabetes were calculated by BMI = Weight (kg) / Height (m^2) formula. The body mass index was evaluated by taking into consideration the classification published by WHO in 2007 for individuals 5-19 years and by the WHO classification arranged in 2004 for individuals 20 years and over. In addition, WHO AnthroPlus program was used to evaluate the z score for 5-19 years [15,16].

In the second part of the questionnaire, information about nutritional label was obtained. In this section of the questionnaire, nutritional label reading status and aims, the level of nutritional label reading, what the individual is paying attention to when reading the nutritional label and choosing the product, the status and purpose of using the packaged and dietary products, the purpose and frequency of using the product for diabetes, and impact of diabetes diagnosis on these choices of participants were determined.

Statistical analysis

The data obtained from the study were analyzed using SPSS version 16.0 program. The Kolmogorov-Smirnov test was used to determine whether the data fit the normal distribution, and chi-square test was used to determine the relationship between the data. Significance level was accepted as $P<0.05$. Quantitative variables were shown as mean ± standard deviation (X ± SD), lower and upper values. Number (n) and percentage (%) values were used for qualitative variables.

Results

The study included 64 female and 41 male type 1 diabetic patients aged between 10-30 years. The distribution of age group, education level, occupational classification and income status of the individuals are shown in Table 1.

54.2% of the participants were older than 18 years (female; 56.3%, male; 51.2%). It was determined that 33.3% of the participants were secondary school graduates. While 29.7% of the females who participated in the study were secondary school graduates, 29.7% were undergraduate graduates, and 39.0% of males were secondary school graduates. 65.7% of the participants (female; 68.8%, male; 61.0%) were students.

The average height and body weight for the ages of 10-18 were 163.4 ± 10.1 cm, 58.4 ± 11.3 kg, respectively, while the average height and body weight for the age of 18 over were 168.8 ± 8.7 cm, 64.7 ± 11.9 kg, respectively.

When z score values of children between the ages of 10–18 years were examined, 79.1% (female; 75.0%, male; 85.0%) were found to be within normal limits. There was no significant difference between z scores of individuals in this age group according to gender ($P > 0.05$). In addition, when BMI values of the individuals over 18 years of age were examined, 70.1% (female; 75.0%, male; 61.9%) were within normal limits. There was no significant difference in BMI values of individuals in this age group according to gender ($P>0.05$).

When the HbA1c values were examined, it was found that 81.6% (for age 10–18 years; 87.2%, for age >18 years; 76.8%) had higher HbA1c values than the target values. On the other hand, 58.8% (64.5% of individuals aged 10–18) and 54.1% of individuals over 18 years of age (68 people) had higher FPG levels than the target levels. HbA1c values and FPG levels was not significantly different according to age groups values ($P>0.05$). In addition, no difference was found between BMI values of those with HbA1c values below and above the target ($P>0.05$).

Table 2 shows the nutritional label use status of patients. It was seen that 85.7% of participants (female; 87.5%, male; 82.9%) read the nutritional label. When causes of reading or not reading of nutritional labels was analyzed, it was found that 29.2% of participants read the labels to apply carbohydrate counting, while 28.5% of participants don't read the food labels because they thought it was not necessary.

88.6% of participants (female; 90.6%, male; 85.4%) had previously received nutritional counseling and nutritional label reading information was given to 67.6% of participants in

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Table 1: Demographic and diabetes characteristics.

Demographic and diabetes characteristics	10–18 age (n = 48)				>18 age (n = 57)				Total (n = 105)			
	Female (n = 28)		Male (n = 20)		Female (n = 36)		Male (n = 21)		Female (n = 64)		Male (n = 41)	
	n	%	n	%	n	%	n	%	n	%	n	%
Level of education												
Literate	2	7.1	2	10.0	–	–	–	–	2	3.1	2	4.9
Primary school	7	25.0	2	10.0	–	–	–	–	7	10.9	2	4.9
Secondary school	19	67.9	15	75.0	–	–	1	4.8	19	29.7	16	39.0
High school	–	–	1	5.0	17	47.2	7	33.3	17	26.6	8	19.4
License	–	–	–	–	19	52.8	9	42.9	19	29.7	9	22.0
Postgraduate	–	–	–	–	–		4	19.0	–	–	4	9.8
Occupational Classification												
Student	27	96.4	19	95.0	17	47.2	6	28.6	44	68.8	25	61.0
Employee	1	3.6	–	–	18	50.0	12	57.1	19	29.6	12	29.2
Not laboring	–	–	1	5.0	1	2.8	3	14.3	1	1.6	4	9.8
Diabetes duration (years)												
<6	12	42.9	6	30.0	14	38.9	6	28.6	26	40.6	12	29.3
6–10	13	46.4	9	45.0	8	22.2	4	19.0	21	32.8	13	31.7
11–20	3	10.7	5	25.0	13	36.1	11	52.4	16	25.0	16	39.0
>20	–	–	–	–	1	2.8	–	–	1	1.6	–	–
Presence of Metabolic Disease												
Yes	5	17.9	4	20.0	9	25.0	3	14.3	14	21.9	7	17.1
No	23	82.1	16	80.0	27	75.0	18	85.7	50	78.1	34	82.9
Presence of Complications												
Yes	2	7.1	1	5.0	3	8.3	2	9.5	5	7.8	3	7.3
No	26	92.9	19	95.0	33	91.7	19	90.5	59	92.2	38	92.7
Received Medical Treatment												
Multi–dose insulin therapy	22	78.6	15	75.0	28	77.8	17	81.0	50	78.1	32	78.0
Insulin pump	6	21.4	5	25.0	8	22.2	4	19.0	14	21.9	9	22.0

counseling (female; 68.8%, male; 65.9%). It was determined that 73.2% of the nutritional label reading information was obtained from dietitians and 25.4% from nurses. In addition, 65.8% (female; 68.8%, male; 61.3%) of the total participants stated that the given information was sufficient.

When sociodemographic characteristics were examined according to nutritional label reading status; it was found that 62.2% of the food label readers and 53.3% of those who did not read were females; 57.8% of the food label readers were over 18 years of age. When education levels are examined, it is determined that 28.9% of food label readers and 60.0% of those who do not read were secondary school graduates, and incomes and expenses of 60.0% of label readers and 73.3% of those who do not read were equal.

It was found that 90.0% of food label readers and 80.0% of those who did not read food label had previously received nutritional counseling. It was observed that 71.1% of food label readers

Table 2: Nutritional label use.

Label Reading	10–18 age (n = 48)				>18 age (n = 57)				Total (n = 105)			
	Female (n = 28)		Male (n = 20)		Female (n = 36)		Male (n = 21)		Female (n = 64)		Male (n = 41)	
	n	%	n	%	n	%	n	%	n	%	n	%
Reading	23	82.1	15	75.0	33	91.7	19	90.5	56	87.5	34	82.9
Not reading	5	17.9	5	25.0	3	8.3	2	9.5	8	12.5	7	17.1
Cause of Nutritional Label Reading	**Female (n = 55)**		**Male (n = 38)**		**Female (n = 97)**		**Male (n = 39)**		**Female (n = 152)**		**Male (n = 77)**	
Curiosity	9	16.4	3	7.9	13	13.4	4	10.3	22	14.5	7	9.1
Increasing product confidence	3	5.5	4	10.5	6	6.2	1	2.6	9	5.9	5	6.5
Buying healthy product	12	21.8	5	13.2	18	18.6	5	12.8	30	19.7	10	13.0
New product	2	3.6	3	7.9	5	5.1	2	5.1	7	4.7	5	6.5
Weight loss product	3	5.5	1	2.6	1	1.0	1	2.6	4	2.6	2	2.5
First consumption	6	10.9	3	7.9	14	14.4	5	12.8	20	13.2	8	10.4
Applying for carbohydrate count	14	25.4	14	36.8	23	23.7	16	41.0	37	24.3	30	39.0
Comparing the products	6	10.9	5	13.2	17	17.6	5	12.8	23	15.1	10	13.0
Cause of not Reading Nutritional Label	**Female (n = 7)**		**Male (n = 6)**		**Female (n = 3)**		**Male (n = 5)**		**Female (n = 10)**		**Male (n = 11)**	
Thinking not necessary	2	28.6	3	50.0	–	–	1	20.0	2	20.0	4	36.3
Being time consuming	1	14.3	–	–	1	33.3	–	–	2	20.0	–	–
Being unclear of ingredients	2	28.6	1	16.6	–	–	1	20.0	2	20.0	2	18.2
Unreadable of letters and numbers	1	14.3	–	–	1	33.3	1	20.0	2	20.0	1	9.1
Because there is no indication of harmful aspects of products	–	–	1	16.6	–	–	1	20.0	–	–	2	18.2
Lack of credible	1	14.3	–	–	–	–	1	20.0	1	10.0	1	9.1
Because reading of parents	–	–	1	16.6	1	33.3	–	–	1	10.0	1	9.1

were given food label reading information while reading information was not given to 53.3% of those who did not read food labels.

Biochemical parameters according to nutritional label reading status are given in Table 3. Accordingly, it was seen that 79.8% of the label readers and 92.9% of those who did not read the label were above the target values of HbA1c. In addition, 56.1% of the label readers and 72.7% of the non-label readers were observed to have higher values than the target fasting plasma glucose levels. However, there were no statistical differences in HbA1c values and FPG levels according to nutritional label reading status of patients ($P > 0.05$).

According to label reading information received, carbohydrate counting, carbohydrate counting stages, and label reading status of participants were shown in Table 4. It was seen that 62.0% of those who were given label reading information knew and applied the carbohydrate count. In addition, it was determined that 75.0% of those who were given label reading information had a carbohydrate count at the 3rd stage, while 63.6% of those who were not given label reading information applied the carbohydrate

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Table 3: Comparison of biochemical parameters according to nutritional label reading status.

Biochemical Parameters	Reading Label		Not Reading Label		Total		χ2 Value	P Value
	n	%	n	%	n	%		
Diabetes Duration (years) (n=105)							0.96	0.81
<6	34	37.8	4	26.7	38	36.2		
6-10	28	31.1	6	40.0	34	32.4		
11-20	27	30.0	5	33.3	32	30.5		
>20	1	1.1	—	—	1	0.9		
HbA1c % (n=103)							1.37	0.45
Target	18	20.2	1	7.1	19	18.4		
Above Target	71	79.8	13	92.9	84	81.6		
FPG (n=68)							0.51	1.33
Under Target	3	5.3	—	—	3	4.4		
Target	22	38.6	3	27.3	25	36.8		
Above Target	32	56.1	8	72.7	40	58.8		

HbA1c: Glycated hemoglobin
FPG: Fasting plasma glucose

count in the first stage. When the carbohydrate count was examined according to label reading status, it was determined that 55.6% of label readers and 33.3% of those who did not read labels knew and applied carbohydrate counting. Also; 66.0% of those who read the label and 40.0% of those who don't read the label applied the carbohydrate count in the 3rd stage.

Discussion

In this study, which aimed to evaluate the nutritional label reading status of individuals with type 1 diabetes, sociodemographic characteristics, diabetic characteristics, anthropometric properties and biochemical parameters, dietary and diabetic product usage conditions and factors affecting product selection were examined.

When nutritional label reading status was examined according to gender, Alpuguz et al. determined that 55.8% of female students and 45.0% of male students read nutritional labels. In another study conducted by Sezek et al., it was seen that 24.1% of female students and 22.2% of male students read nutritional labels. In addition, in both studies, it was found that female students read nutritional label significantly more than male students [17,18]. In the study conducted by Ozgul and Aksulu (2006), it was found that there was no difference between nutritional label reading and gender during the 1995 period, whereas in 2005, females showed more attention to label information than males [19]. In this study, nutritional label reading rate was 89.1% for females and 85.3% for males unlike other studies. No significant difference was found between sex and nutritional label reading status. There was no similarity between the previous studies on gender and nutritional label reading status and this study.

In some studies, relationship between education levels and nutritional label reading habits was investigated. Accordingly, it was found that as the level of education increases, the level of nutritional label reading increases parallely [12,19].

It has been shown that nutritional label reading status differed significantly according to age in many studies [12,19,20]. Additionally, in the study conducted by Coskun and Kayisoglu (2016), it was determined that according to participants

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Table 4: Evaluation of CHO count and CHO count stages according to nutritional label reading information and label reading status.

Carbohydrate Count	Informed about label reading (n=71)		Not informed about label reading (n=34)		Total (n = 105)		χ2 Value	P Value
	n	%	n	%	n	%		
Unknows	4	5.6	14	41.2	18	17.1	21.057	**0.0001**
Knows but not applies	23	32.4	9	26.5	32	30.5		
Knowing and applying	44	62.0	11	32.3	55	52.4		
Carbohydrate Count Stage	**Informed about label reading (n=44)**		**Not informed about label reading (n=11)**		**Total (n = 55)**			
	n	%	n	%	n	%		
1. Stage	3	6.8	7	63.6	10	18.2	20.089	**0.0001**
2. Stage	8	18.2	2	18.2	10	18.2		
3. Stage	33	75.0	2	18.2	35	63.6		
Carbohydrate Count	**Reading Label (n = 90)**		**Not Reading Label (n = 15)**		**Total (n = 105)**		**χ2 Value**	**P Value**
	n	%	n	%	n	%		
Unknowing	13	14.4	5	33.3	18	17.1	3.935	0.14
Knowing but not applying	27	30.0	5	33.3	32	30.5		
Knowing and applying	50	55.6	5	33.3	55	52.4		
Carbohydrate Count Stage	**Reading Label (n = 50)**		**Not Reading Label (n = 5)**		**Total (n = 55)**			
	n	%	n	%	n	%		
1. Stage	8	16.0	2	40.0	10	18.2	1.933	0.38
2. Stage	9	18.0	1	20.0	10	18.2		
3. Stage	33	66.0	2	40.0	35	63.6		

P < 0.001

the reasons for reading the nutritional label were 74.4% health, 14.5% learning the content, 6.9% solving the weight problem, and 3.2% of participants had other reasons [20]. However, in this sutdy, it was seen that nutritional label reading status didn't differ according to age groups. In addition, it was found that 29.2% of participants read the labels to apply carbohydrate counting.

In a study in which consumers' attitudes and behaviors were examined, 68.0% of the participants stated that they read the nutritional label when they purchased the new product and 67.0% of them read the nutritional label when buying the product for the first time or when buying a product they did not buy frequently. In addition, the reasons for the participants to read the nutritional label always and often were comparing two different products (62.0%), having a food-related health problems (61.0%), maintaining / fitting their forms (60.0%), and losing weight (58.0%) [21]. In this study, the reasons why the participants to read the nutritional label were applying carbohydrate count (72.8%), comparing products (45.9%), curiosity (32.6%), purchasing the product for the first time (31.5%), increasing product confidence (16.3%), and purchasing a slimming product (7.6%). When the reasons for reading the nutritional label were examined, similar results were reached with previous studies. It was found that participants generally read the nutritional label for health related issues.

In the study where consumers' attitudes and behaviors towards nutritional labels were

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investigated, it was noteworthy that 32.1% of the participants think it was not required to read nutritional labels [12]. As a result of this research, it was found that the reason for not reading the nutritional label was not considered necessary at the rate of 46.2% and that the content was not understandable at the rate of 30.8%. The reason for not reading the nutritional label was similar to the previous studies. It was found that most of the participants did not read the nutritional label because they did not think it was necessary. In this study, the label reading rate of individuals with Type 1 diabetes was 85.7%. This differs according to having additional metabolic disease. In addition to type 1 diabetes, 90.4% of the individuals with hypothyroidism and other metabolic diseases such as celiac are reading labels, while the rate of label reading is 86.9% for individuals without additional metabolic diseases.

There was no significant difference between label reading status and the presence of additional metabolic disease and did not show any similarity with previous studies. This may be due to insufficient number of participants with metabolic disease in addition to type 1 diabetes.

In a case-control study conducted by Fitzgerald et al. (2008) of 100 type 2 diabetic and 101 healthy individuals, it was reported that the artificial sweetened sweet and drink consumption of diabetic individuals was more frequent than the control group [22]. In this study, the use of diabetic products was 43.8% (46.7% of nutritional label readers) and no significant relationship was found between age, sex, and duration of diabetes. It was found that 53.3% of the participants used diabetic products to balance blood sugar and 73.3% preferred diabetic beverages the most. Diabetic product usage of diabetic individuals shows similarity in the studies due to its high availability in the market, frequently recommended to people with diabetes, and advertisements [22].

In a study conducted by Kollannoor-Samuel et al. between 2006 and 2010, 12 months of intervention by community health workers on 203 people (100 people type 2 diabetes, 103 people healthy) to determine the effect on nutritional label use and to investigate the effect of nutritional label use and dietary quality on glycemic control, the use of nutritional labels was higher than the control group [23].

Conclusions

In this study, nutritional label reading status of individuals with Type 1 diabetes and factors affecting nutritional label reading status were examined and their attitudes and behaviors towards nutritional labeling are revealed. Nutritional labeling has an effect on the metabolic control of individuals with Type 1 diabetes, thus preventing complications and reducing the risk of additional metabolic diseases. In this context, reading the labels of foods consumed by people with Type 1 diabetes will contribute to the regulation of blood sugar and prevent problems related to diabetes in the long term. In order to increase this awareness, the importance of nutritional label reading should be mentioned in medical nutrition treatment and diabetes education. Making nutritional labels more readable and understandable will reduce the difficulties in reading labels and will be effective in raising awareness about this.

Conflict of Interest

The authors declare no conflict of interest.

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Original Research

Colorectal cancer in patients with diabetes mellitus

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Abstract

Background and Aims: Diabetes mellitus (DM) and colorectal cancer are two common diseases, with a growing trend and the major causes of mortality and morbidity, with a negative impact on life expectancy and quality of life, with socio-economic impact, which makes them a major public health problem. DM is the etiopathogenic factor involved in several diseases, including cancer. There are numerous studies on DM as a risk factor for breast, endometrial, pancreatic, liver cancer, non-Hodgkin's lymphoma, but also colorectal cancer. **Material and Method:** The study includes patients hospitalized in the Gastroenterology Department for digestive symptoms who after a colonoscopic and bioptic examination were diagnosed with colon/rectal adenocarcinoma and who were subsequently hospitalized in the General Surgery Department for surgery. Patients were divided into two groups: with and without diabetes mellitus. All patients in the study followed the same oncological protocol and were monitored dynamically at 3-6-9-12 months after diagnosis. **Results:** Diabetic patients were frequently associated with obesity and a more advanced stage of the oncological disease (DM – stage I:20%, stage II: 24%, stage III: 36%, stage IV: 20%; non-DM – stage I: 23%, stage II 28.2%, stage III: 34.7%, stage IV: 14.1%). No major differences were observed among diabetic patients regarding the type of antidiabetic treatment and the stage of the disease. Postoperative complications were more common in diabetic patients (24%), and the survival rate was slightly lower among patients with DM (80%). **Conclusions:** The long-term survival of colorectal cancer patients who have received surgical treatment depends on the stage of the disease, the patient's age, and the associated pathologies. DM brings additional contributions to oncological risk, being a risk factor for the oncological process in general and for colorectal cancer in particular.

Keywords: Colorectal cancer, connection, diabet mellitus, follow-up.

Background and Aims

Diabetes mellitus (DM) and colorectal cancer (CRC) are diseases with an increasing impact on the population; DM representing the disease of the century with a global prevalence that has doubled since 1980, increasing from 4.7–8.5 in the adult population. type 2 DM accounts for 90–95% of all cases of DM worldwide, totaling about 191 millions, in 2002 [1, 2]. In an important measure, but of a smaller magnitude, the prevalence of CRC is on the rise, being the third most common cancer and the second most common cause of cancer mortality at the global level [3].

Epidemiological studies suggest a link between type 2 DM and CRC. People with DM have a higher risk of developing cancer and at the same time have a higher mortality rate [4]. DM and CRC have in common a number of general

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risk factors prevalent in populations where a Western lifestyle is prevalent (diet high in animal fats and poor in vegetables/fruits, high consumption of red meat, refined carbohydrates; sedentary lifestyle, obesity) [5]. Obesity and diabetes are epidemiologically associated with cancer risk, and both together, but also separately, are demonstrated risk factors for cancer in general and for CRC in particular [6, 7].

The number of deaths from DM and CRC has increased by up to 90%and 57%, respectively, in the last 20 years at the global level [1]. The risk of developing CRC in diabetic patients was estimated to be 27% higher than in non-DM patients [8]. Early detection of DM and CRC substantially increases the chances of treatment and survival. More than a third of deaths from CRC could be prevented by a rigorous screening program for people at high risk for cancer. Strategies to promote the prevention and early detection of these diseases are urgently needed [9].

Material and Method

This study refers to patients admitted to the Gastroenterology Department of the Emergency Hospital of Constanta, who underwent a colonoscopic and bioptic examination and were diagnosed with CRC and who needed hospitalization in the Department of General Surgery in order to perform surgery, during January 2017–2019. For 103 of the patients, the biopsy showed colonic or rectal adenocarcinoma; 25 of these patients had associated DM.

Patients were hospitalized in the GastroeterologyDepartment for digestive symptoms (transit disorders: constipation/diarrhea, abdominal pain, rectorage), with or without alteration of the general condition (fatigue, marked weight loss, anemia). As landmarks we evaluated the following: age, gender, body mass index (BMI), smoker status, alcohol consumption, type of patient's diet, first symptom. In patients with DM, we also evaluated: the duration of the disease, the type of treatment (insulin or oral antidiabetics drugs: OADs), the duration of treatment, the complications caused by the disease. From a biological point of view, we evaluated: blood glucose value, glycosylated hemoglobin, tumor markers (CEA, CA 19-9).

All patients in the study had as recommendations: oncological and surgical consultation, complementary imaging explorations for staging. The patients were followed in dynamics, and after the surgery, visits were performed at 3-6-9-12 months, establishing the stage of the disease, the type of oncological treatment, the survival rate. Of the 103 patients enrolled in the study, patients were divided into two groups: with DM and non-DM.

Results

Between January 2017–2019, 103 patients were diagnosed with colon or rectal adenocarcinoma, with histopathological confirmation. Patients were divided into two groups: with DM (25) and non-DM (78). In both groups the sex ratio was inclined in favor of men, the median age of those associated with DM (68) was higher compared with those non-DM (66.5). Most DM patients come from rural areas (60%), a possible fact for the delayed presentation to the doctor, for the deficient control of DM; the patients being in an area considered as disadvantaged of the country. The most common first symptom in the group with DM was abdominal pain (44%), followed by transit disorders (24%); conversely compared to non-DM patients (abdominal pain: 29.48%, intestinal transit disorders: 44.87%). Abdominal discomfort and abdominal pain usually occur in a more advanced stage of the disease, initially appearing changes in bowels habits (like: frequencies, color, shape, constipation or diarrhea) that send the patient to the doctor in time [10].

In both groups most of the patients developed colon adenocarcinoma (DM: 80%, non-DM: 73.07%) and in 20% of the cases, they developed rectal adenocarcinoma. There were also patients who had previously other cancers, such as breast, stomach, prostate, lung cancer, but also patients with metachronous cancer (DM: 8%, non-DM: 3.84%). Six of the non-DM patients had a family history of CRC. Diabetic patients associated: obesity (median BMI = 30.02 kg/m^2), compared to

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Table 1: Clinical data of the patients with or without DM.

		DM	Non-DM	Total
Overall (no, %)		25 (24.27%)	78 (75.73%)	103(100%)
Gender	Men	16(64%)	41(52.56%)	57(55.34%)
	Women	9(36%)	37(47.44%)	46(44.66%)
Age (years, median)		51–85 (68)	38–86 (66.5)	36–86 (67)
Environment	Urban	10 (40%)	58 (74.35%)	68 (66.01%)
	Rural	15 (60%)	20 (25.65%)	35 (33.99%)
The first symptom	Abdominal pain	11 (44%)	23 (29.48%)	34 (33.01%)
	Intestinal transit disorders	6 (24%)	35 (44.87%)	41 (39.8%)
	Rectal hemorrhage	5 (20%)	13 (16.66%)	18 (17.47%)
	Anemia	1 (4%)	3 (3.84%)	4 (3.88%)
	Weight loss	2 (8%)	4 (5.12%)	6 (5.82%)
Colon cancer		20 (80%)	57 (73.07%)	77 (74.75%)
Rectal cancer		5 (20%)	21 (26.93%)	26 (25.25%)
Other cancers	Metachronous	2 (8%)	3 (3.84%)	5 (4.85%)
	Breast	0	4 (5.12%)	4 (3.88%)
	Prostate	1 (4%)	3 (3.84%)	4 (3.88%)
	Pulmonary	0	1 (1.28%)	1 (0.97%)
	Gastric	0	1 (1.28%)	1 (0.97%)
	Another location	0	0	0
Family history of cancer		0	6 (7.69%)	6 (5.82%)
BMI (kg/m^2), median		21.91–49.67 (30.02)	17.3–39.84 (25.49)	17.03–49.67 (27.04)
Hypertension		19 (76%)	11 (14.1%)	30 (29.12%)
Smokers		7 (28%)	12 (15.36%)	19 (18.44%)
Alcohol consumers		4 (16%)	7 (8.97%)	11 (10.67%)

25.49 kg/m^2 in non-DM patients), hypertension (DM: 76%, non-DM: 14.1%) and higher tobacco use (>10 cigarettes/day, >10 years) and alcohol (high consumption) (Table 1).

All patients with DM had type II, 68% being treated with OADs (with a median time of 7 years) and 32% with insulin (with a median time of 11 years). From personal history we found that 20% of patients suffered from diabetic neuropathy, 12% from diabetic nephropathy and 4% from diabetic angiopathy (Table 2).

All patients diagnosed with rectal adenocarcinoma received preoperative radiotherapy and neoadjuvant chemotherapy. All patients underwent surgery. Postoperative complications were more common in patients with DM, who had a slower cure (24%) than in non-MD patients (5.12%). Regarding staging, diabetic patients were diagnosed in an advanced stage of the disease. Postoperatively, no patient received radiotherapy, according to the protocol 68% of diabetics received chemotherapy and 62.83% of non-MD. (Table 3.)

After the surgery, the patients were followed at 3-6-9-12 months by medical visits or by telephone, when: their general condition, paraclinical examinations performed postoperatively in dynamics (tumor markers, computed

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tomography), and the appearance of possible complications/secondary determinations was evaluated. Survival at 1 year is higher in the group of non-DM patients (85%) than in patients with DM (80%) (figure 1).

Table 2: Characteristics of patients with DM and CRC.

Patients with DM And CRC		
The type of diabetes	Type 1	0
	Type 2	25
The type of treatment	No treatment	0
	OADs	17 (68%)
	Insulin	8 (32%)
Duration of disease	No treatment	0
	OADs (years, median)	1–15 (7)
	Insulin (years, median)	2–30 (11)
Complications	Diabetic angiopathy	1 (4%)
	Diabetic retinopathy	2 (8%)
	Diabetic neuropathy	5 (20%)
	Diabetic nephropathy	3 (12%)
	Skin infections	1 (4%)
	Without complications	13 (52%)

Discussion

A 2010 report by the American Diabetes Association recognizes the link between DM and CRC [11]. Patients with DM have a 30% higher risk of developing CRC compared to non-DM patients, with similar results for both sexes [8]. Risk factors such as obesity, tobacco use and alcohol are involved in the development of DM and CRC. Overweight and obese patients have a higher risk of developing DM. Studies have shown that DM and obesity are proven risk factors for cancer in general and for CRC in particular. Obesity control through measures to prevent/reduce overweight can become a relevant method in reducing the risk of developing DM and implicitly CRC [12–15].

Cancer shares with obesity and DM a common metabolic and humoral environment (proinflammatory cytokines, hyperinsulinism, elevated serum IGF-1 levels). Obesity and DM are often associated, but the overlap is not perfect. Current epidemiological data show that DM is associated with most obesity-related cancers, but the link is much closer to DM, suggesting that DM makes additional contributions to cancer risk

Table 3: Pre/postoperative staging and treatment management in patients with/without DM.

	DM	NON-DM	TOTAL
Overall (no, %)	25 (24.27%)	78 (75.73%)	103 (100%)
Neoadjuvant oncological treatment			
Without treatment	20 (80%)	57 (73.07%)	77 (74.75%)
Chemotherapy	5 (20%)	21 (26.93%)	26 (25.25%)
Radiotherapy	5 (20%)	21 (26.93%)	26 (25.25%)
Surgical treatment			
Yes	25 (100%)	78 (100%)	103 (100%)
No	0	0	0
Postoperative complications			
Wound infection	2 (8%)	4 (5.12%)	6 (5.82%)
Pneumonia	1 (4%)	1 (1.28%)	2 (1.94%)
Hydroelectrolyte imbalance	2 (8%)	3 (3.84%)	5 (4.85%)
Slow healing	6 (24%)	4 (5.12%)	10 (9.7%)
Staging			
Stage I	5 (20%)	18 (23%)	23 (22.33%)
Stage II	6 (24%)	22 (28.2%)	28 (27.18%)
Stage III	9 (36 %)	27 (34.7%)	36 (34.95%)
Stage IV	5 (20%)	11 (14.1%)	16 (15.53%)
Adjuvant oncological treatment			
Without treatment	8 (32%)	29 (37.17%)	37 (35.92%)
Chemotherapy	17 (68%)	49 (62.83%)	66 (64.08%)
Radiotherapy	0	0	0

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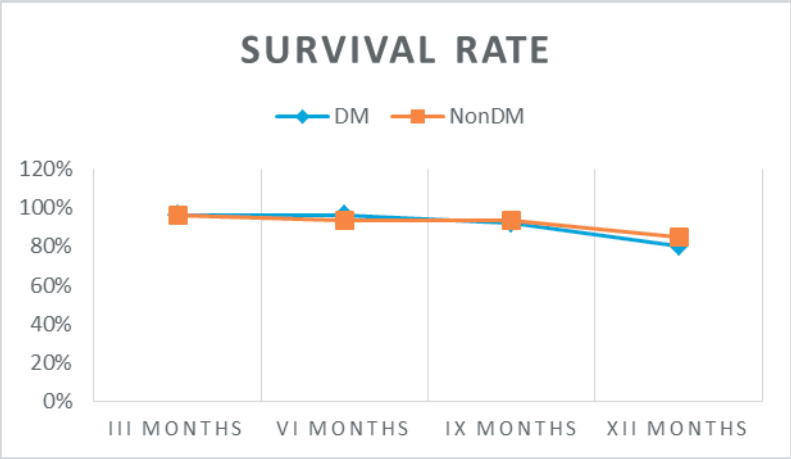

Figure 1: Survival rate in DM patients compared to non-DM patients in the first year of surveillance.

[16]. In our study, DM patients also had associated obesity, median BMI: 30.02 kg/m^2.

Other risk factors for DM and CRC are tobacco and alcohol consumption. There are prospective studies that have shown that smoking is a risk factor in the development of DM [17]. Tobacco use also increases the risk of developing adenomatous polyps that are precursors of CRC lesions and in current studies is considered to be a risk factor for CRC [18]. Intense alcohol consumption has been associated with an increased risk of developing DM and also increases the risk of developing CRC [19, 20]. Tobacco and alcohol consumption is also found in patients in our study (28% smokers, 16% alcohol users) in diabetic patients, in a much higher percentage than non-DM (15.36% smokers, 8.97% alcohol users).

An additional hypothesis to explain the association between DM and CRC is slowed intestinal transit, a common complication in diabetics due to diabetic neuropathy (which causes elevated concentrations of secondary bile acids in the stool with carcinogenic potential) and which is associated with elevated blood glucose levels and triglycerides. Although this explanation is not prevalent in the pathophysiological explanations of CRC, its scientific relevance is supported by data from the literature, demonstrating on an animal model that fecal bile acids can lead to CRC [21–23].

From a biological point of view, a relationship between DM and CRC can be established. Patients with type II DM in the early stages of the disease are characterized by elevated insulin concentrations, which have also been associated with colorectal cancerogenesis. Endogenous hyperinsulinemia, which occurs in the early stages of diabetes as a compensatory phenomenon for peripheral insulin resistance, develops after frequent exposure of obese patients to elevated circulating levels of glucose and lipids. How insulin produces intracellular signals differs between individuals with DM and healthy individuals; insulin resistance causes metabolic signaling to be altered while maintaining and increasing proliferative signals. Thus, excess endogenous insulin in DM patients by amplifying antiapoptotic and pro-mitogenic signals may initiate or maintain an oncogenic process [24].

The mechanisms of oncogenesis, from the existing data in the literature, involve several levels: hyperglycemia may promote pathogenic mechanisms, and there is a recent link between hyperglycemia and increased incidence of CRC (but also gastric and endometrial cancer) and mortality from CRC. All these data must be looked at with caution because beyond a plausible biological point of view, is the fact that oncogenesis in CRC involves a long period of action of risk factors [24, 25].

The treatment of patients with DM consists of a wide range of drugs; often a patient may change their dose or type of medication over the years or receive more than one medication at a time. The potential role of these drugs in favor of cancer is unclear, but most likely is minor, if exists [26, 27].

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Considering that the appearance of CRC is preceded by a long period of exposure to carcinogenic risk factors (20–30 years), the duration of insulin treatment was studied as an important contributor to the role of insulin risk factor and it was concluded that there is a higher risk of developing CRC within 5 years of diagnosing DM. Also, by comparing patients with insulin treatment to those without insulin, a double increase in the risk of CRC can be observed in the first category [28–30]. Most diabetic patients in our study received treatment with OADs (68%) and had a median time of treatment of seven years. Patients treated with insulin had a median time of 11 years, so the treatment of patients with DM may be an associated risk factor for CRC.

Considering that DM is an underdiagnosed disease, when it comes to the time of exposure of patients to DM, confusion can occur. Many patients are diagnosed at the onset of symptoms, not after screening. Regarding oncological treatment in patients with DM and CRC, there is no evidence to support specific approaches to chemotherapy and no benefits have been observed during survival [31]. Patients in stages II and III who received adjuvant chemotherapy and associated DM had a higher recurrence and a higher mortality rate than patients without diabetes [32]. Thus, short- and long-term mortality in patients combining CRC and DM is higher than in patients with CRC and non-DM. The data from our study are similar to the literature, comparing the survival of DM patients with those without DM, the 1-year survival rate being 80% in DM patients and 85% in non-DM patients.

Conclusions

DM is a risk factor for CRC involved in both the early and the advanced stages of oncogenesis, but more than that it is also an important prognostic factor. National guidelines do not include DM as a risk factor for screening for CRC, although the increased risk for colorectal adenomas in DM patients is similar to the risk of personal history of colorectal adenomas or the risk associated with the presence of a first-degree relative with CRC. We consider that colonoscopic screening in patients with DM is required as a major part of the measures aimed at decreasing the prevalence of CRC. The wide recognition in the medical world of the connection between the two sufferings with increasing prevalence is a necessary premise for the containment of the phenomenon at a global level.

Conflict of Interest

The authors declare no conflict of interest.

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Original Research

Nutritional status and risk of diabetes mellitus type 2 among medical students

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Abstract

Background and Aims: The phenomenon of the 21st century is a significant predominance of obesity in most countries. The metabolic effects of obesity (impaired glucose tolerance, type 2 diabetes mellitus (T2DM), hyperlipidemia, and hypertension) correlate more closely with abdominal obesity. **Purpose** is to investigate the features of nutritional status and the risk factors of the developing of T2DM in medical students. **Material and Methods:** 200 young medical students I-VI courses (according to WHO classification) were investigated. There were 140 Ukrainians and 60 - foreigners (Arabian). Physical examination (anthropometry), tonometry, anamnesis assessing, including data on the risks of the development of diabetes mellitus (DM) (Findrisk scale), and statistical methods were used. **Results:** Among the risk factors there are violations of the nutritional status, despite the students being sufficiently informed about the harmfulness of the use of fast food, alcohol consumption, insufficient physical activity (especially in Ukrainians), family history of type 2 diabetes mellitus (T2DM) (especially in foreigners) and having continuous stress were found to be the most significant. Almost most of foreign students consume alcohol and are smokers. That is a fairly high rate for medical students who are well aware of the harmfulness and consequences of alcohol abuse and smoking. Reducing the risk of developing T2DMand CVD is possible when changing modifiable risk factors, such as nutrition, physical activity, stress and deliverance of bad habits, such as smoking and drinking alcohol. **Conclusions:** 1. Most Ukrainian and foreign medical students have various risk factors of developing T2DM. Despite medical students being sufficiently informed about the harmfulness of consuming fast food, the risk factors were found to be one of the most significant. 3. Among risk factors of T2DMare excess weight and obesity as result of violations of the nutritional status, alcohol consumption, smoking (especially in foreign students), insufficient physical activity (especially in Ukrainian students) and family history of T2DM (especially in foreign students).

Keywords: medical students, obesity, risk factors, diabetes mellitus type 2, nutrition.

Background and Aims

The phenomenon of the 21st century is a significant predominance of obesity in most countries [10, 12]. Obesity is the most common risk factor for many serious medical problems that lead to decrease in the quality of life, a significant increase in morbidity and premature death [6, 8].

The American Association of Clinical Endocrinology and the American College of Endocrinology has proposed a new name for obesity in 2016, namely Adiposity-Based Chronic Disease. This name does not replace the term of "obesity", but it helps the doctor, regardless of specialty, to focus more upon the physio-pathological implications of excess weight [10].

At present it has been proved that adipocytes of various fat depots can differ in size and response to hormones [1, 5]. And the first proof is the fact that in men fat is deposited mainly on the abdomen whereas in women it is deposited in the lower torso. It is well known that the metabolic effects of obesity (impaired glucose tolerance, type 2 diabetes mellitus (T2DM), hyperlipidemia,

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hypertension) correlate more closely with the obesity of the upper half of the body (so-called abdominal or android) than the lower (femoral) [3, 8–11].

The relationship of obesity with disorders of carbohydrate metabolism, including T2DM, continues to be of great interest, primarily because of the need to develop effective approaches to the prevention of target organs and cardiovascular and kidney damage, since to date, the existence of common mechanisms for the formation of cardiovascular complications and nephropathies of metabolic nature have been proved [2, 4, 7, 12]. **Purpose** is to investigate the features of nutritional status and the risk factors of the developing ofT2DM in medical students.

Material and Methods

A total of 200 young medical students, I-VI courses (according to WHO classification), were investigated. There were 140 Ukrainians and 60 - foreigners (Arabian). The average age was 21.0 (18.0; 25.0) years for Ukrainian students and 23.0 years (20.0; 29.0) for foreign students. Among the persons there were 67 men (47.8%) and 73 women (52.2%) - Ukrainian students; and 35 men (58.3%), and 25 women (41.7%) for foreign students.

The studies were conducted according to the developed program with careful evaluation of anamnestic, general clinical, and laboratory parameters.

An assessment was made from the history of life, the family history of diseases, the cardiovascular system, and T2DM. Certain complaints were collected that indicated the risk of the development of these pathologies. Anthropometry was performed. Body mass index (BMI) was defined as the ratio of body weight (kg) divided to square height (m^2). Waist circumstance was measured in the middle of the distance between the edge of the lower rib and the sacrum os ilium.

The nutritional status of each subject was evaluated. Students were surveyed and assessed on the find risk scale - risk assessment of T2DM. Statistical processing of research results was carried out by the methods of variation statistics implemented by the standard package of applications "STATISTICA® 6.1", serial number of the license AGAR 909E415822FA; Medcalc® Version 12.7.0.0.; Microsoft Excel.

The Kolmogorov-Smirnov single-assembly test was used to test the hypothesis of normal distribution. When describing quantitative characteristics, the median (Me) and interquartile scale (25%, 75%), for qualitative signs - in relative values are determined.

Results and Discussion

In the studied groups of students among Ukrainian (n = 140) the average body weight was 75.6 kg (55.0; 98,0). 22.1% (31 people) of students had obesity 1-3 degree (for WHO classification) [8], 15.0% (21 students) were overweight. Median BMI was 24.1 (21.5; 32.4) kg/m^2.

Among foreign students (n = 60), normal body weight was found in 21.6% (13 people), overweight – 18.4% (11 people) and obesity 1–3 degree - 60.0% (36 people). Median BMI was 28.1 (25.6; 36.4) kg/m^2. The average WC for Ukrainian students was 79.1 (55.4; 110.2) sm. At 37.1% (52 people) waist size is above the normal that confirms abdominal type. For foreign students the WC exceeds the normal levels in 65% (39 people). This indicates that the problem of overweight and obesity is more frequent among foreign students.

None of the students had a history of stable antihypertensive therapy or increased glycemia.

Among the risk factors for T2DM in Ukrainian students in the first place was violation of the nutritional status. Risks factors of T2DM among Ukrainian students are below:

1. Not eating vegetables and fruits daily – 40% (56 people).
2. Eating fast food: every day – 2.1% (3 person); once a week - 35% (49 people); once a month – 23.6% (33 people); very rarely – 37.9% (53 people).
3. The students who eat fast food depend on their mood – 62.9% (88 people).
4. The percent of people informed about the hazards of fast food is 97.8% (137 people).

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5. Alcohol users (from once a week to once a month) consist 72.8% (102 people).
6. Smokers were 17.1% (24 people).
7. Do not do any daily physical activity – 51.4% (72 people).
8. 85% of students (119 people) were stressed.
9. Family history of T2DM was identified in 37.1% (52 people) of the respondents. A family history of cardiovascular diseases was detected in 82.8% (116 people) (table 1).

For foreign students, statistics looks a little different, but in the first place still is a violation of the nutritional status. Risks factors of T2DM:

1. Not eating vegetables and fruits daily - 63.3% (38 people).
2. Eating fast food: every day - 18.3% (11 people); once a week – 51.7% (31 people); once a month – 6.7% (4 people); very rarely – 23.3% (14 people).
3. The number of subjects who consume fast food depends on their mood – 25 % (15 people).
4. The people informed about the hazards of fast food – 90 % (54 students).
5. Alcohol users (from once a week to once a month) were 91.7% (55 people).
6. Smokers – 81.7% (49 people).
7. Do not do daily physical activity – 26.7% (16 people).
8. 95% of students have stress (57 people).
9. Identified family history of T2DM in 71.7% (43 people) of the respondents; family history of cardiovascular diseases was detected in 30% (18 people).

Thus, many Ukrainian and foreign medical students have the various risk factors of developing T2DM. Despite the students being sufficiently informed about the harmfulness of the use of fast food, among the risk factors are violations of the nutritional status, alcohol consumption, insufficient physical activity (especially at Ukrainians), family history of T2DM (especially at foreigners) and having continuous stress were found to be the most significant. Most of the foreign students consume alcohol and are smokers. That is a fairly high rate for medical students who are well aware of the harmfulness and consequences of alcohol abuse and smoking. Reducing the risk of developing T2DM and CVD is possible when changing modifiable risk factors, such as nutrition, physical activity, stress and deliverance of bad habits, such as smoking and drinking alcohol.

Conclusions

1. Most Ukrainian and foreign medical students have various risk factors of developing T2DM.

Table 1: Characteristics of the main risk factors T2DMamong medical students.

Marker, %	Ukrainian, n = 140	Foreign, n = 60
Not eating vegetables and fruits daily	40%	63.3%
Eating fast food: every day	2.1%	18.3%
Once a week	35%	51.7%
Once a month	23.6%	6.7%
Very rarely	37.9%	23.3%
Students who use fast food depends on their mood	62.9%	25 %
The percent of people informed about the hazards of fast food	97.8%	90 %
Alcohol users (from once a week to once a month)	72.8%	91.7%
Smokers	17.1%	81.7%
Do not make daily physical activity	51.4%	26.7%
Stable stressed	85%	95%
Identified family history of T2DM	37.1%	71.7%

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2. Despite the medical students being sufficiently informed about the harmfulness of the using fast food, the risk factors were found to be one of the most significant.
3. Among risk factors of T2DMare excess weight and obesity as result of violations of the nutritional status, alcohol consumption, smoking (especially in foreign students), insufficient physical activity (especially in Ukrainian students) and family history of T2DM (especially at foreign students).
4. To prevent the development of T2DM, it is necessary to conduct a survey of medical students on the risk factors of DM (Findrisc score), identify symptoms of stress, and give recommendations of lifestyle modification.

Conflict of Interest

The authors declare no conflict of interest.

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Original Research

Dietary pattern of long-distance runners and its effect on their body composition and performance

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Abstract

Background and Aims: Evaluation of a player's dietary intake is important both for training and research. Along with body composition it provides an insight into their positive adaptation to training. This study aimed at assessing the effect of the nutritional profile of Indian long-distance runners on their body composition and performance. **Material and Method:** Dietary intake of 53 Indian long-distance runners was assessed using 24 hours dietary recall method. Body composition was analyzed using bioelectrical impedance analysis. Performance was assessed through indirect measurement of VO2 max using Astrand protocol. **Results:** BMI was correlated positively with energy and fat intake ($p < 0.05$). Sum of skinfolds was correlated positively with fat intake and energy intake (only among males) ($p < 0.05$). Fat % was correlated positively with energy intake, carbohydrate intake, fat intake (only among females) ($p < 0.05$) and negatively with VO2 max though not significant. Fat free mass % was negatively associated with energy and carbohydrate intake ($p < 0.05$). Association of VO2 max was significantly positive with protein, calcium and iron intake and negative with carbohydrate intake ($p > 0.05$). Energy intake was significantly positively correlated with carbohydrate intake for the group as a whole and with fat intake specifically in females ($p < 0.05$). Fat free mass had significant negative correlation with energy, carbohydrate intake, and fat intake in females. Inverse association of fat free mass % and VO2 max was also observed though non-significant in both males and females. **Conclusions:** Dietary intake has an impact on both body composition and VO2 max. Body weight, fat, and fat free mass distribution in long distance runners can be managed through diet and can form an important part of athletic development.

Keywords: BMI, energy balance, nutritional profile, training.

Background and Aims

Sports nutrition has an important role to play in athletic development. It helps in attainment of sports specific physique and body composition and also aids in proper and timely recovery from fatigue induced from strenuous training regimes. Hence, it is very important to include balanced dietary intake as one of the fundamental objectives of athletic training [1]. In one of its consensus statements, the International Association of Athletic Federations (IAAF) states that "Well-chosen foods will help athletes train hard, reduce risk of illness and injury, and achieve performance goals, regardless of the diversity of events, environments, nationality, and level of competitors" [2]. Long distance runners in particular require higher nutrient intake because of their longer training durations leading to an increased energy turnover and metabolic adaptations [3]. Despite this fact, it has been found that nutritional intake of athletes worldwide is subnormal [4–6]. No study has been reported on elite Indian long-distance runners related to their dietary patterns and its overall impact on their health and performance. However, among a varied group of Indian athletes, it has been found that their macronutrient and micronutrient

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intake is below the recommended levels [7–10]. Following this, three main objectives were set for the study: (1) to study the dietary pattern of Indian long-distance runners, (2) To find the relationship of dietary intake with their body composition, (3) To study the association of VO2 max with dietary intake and body composition.

Material and Method

Study design and participants

A cross-sectional study was conducted on 53 (27 males and 26 females) state and national level Indian long-distance runners during their preparatory phase, after informed consent.

Laboratory, anthropometric, and nutritional data collection

Nutritional intake of players was assessed using 24 hours dietary recall method and was compared against Indian Council of Medical Research (ICMR)'s Nutrient Requirements & Recommended Dietary Allowances for Indians (2010) [11]. Intake assessment and calculations were done using the software "DietSoft" (version 1.2.0; 2008–2009; Department of Dietetics; AIIMS & Invincible IDeAS Co., India). Body composition was analyzed using SECA Body Composition Analyzer. Anthropometric measurements were taken using standardize GPM anthropometric kit and Holtain skin fold caliper and followed International Society for Advancement of Kinanthropometry (ISAK) protocol [12]. The measurements included height, weight, triceps skin fold, biceps skinfold, subscapular skin fold, and suprailiac skin fold. Performance was expressed in terms of maximal oxygen uptake VO2 max calculated using bicycle ergometer test following Astrand Protocol (1954) on Monark LC7 bicycle ergometer [13].

Statistical analysis

Sample size was calculated using mean and standard deviation from previous studies. IBM SPSS 20 was used for statistical analysis. The data was checked for normality and homogeneity followed by calculation of descriptive statistics. Pearson's correlation coefficient and linear regression were performed to study the association between the variables under study.

Results

The participants consisted of 27 males and 26 females. Mean age of the players was 18.17 ± 2.90 years, mean height was 165.75 ± 9.75 cm, and mean weight was 53.56 ± 8.61 Kg. Descriptive statistics for anthropometric parameters and VO2 max have been represented in tables 1 and 2.

The first objective of the study was to study the dietary pattern of Indian long-distance runners. The average daily energy intake, carbohydrate, fat, protein, calcium, and iron intake was assessed for the same (tables 3 and 4). Mean percentage adequacy was also calculated using the formula:

$$\text{MPA}\left(\text{Mean percentage adequacy}\right)=\frac{\text{daily intake}}{\text{recommended dietary allowance by ICMR}}\times 100$$

It was seen that MPA was low for total energy and carbohydrate in both males and females. On the other hand, fat intake has been found considerably high. MPA was more than optimum for protein, calcium, andiron for both the genders.

To accomplish the second and third objective, Pearson's correlation coefficient was calculated as shown in table 5–7 and the associated variables were further analyzed through linear regression. In anthropometric parameters, a significant positive correlation of BMI was found with sum of skinfolds (SSF) and fat % and negative with fat free mass % (FFM). SSF was positively correlated with fat % and negatively with FFM ($p<0.05$). FFM had significant negative correlation with BMI and SSF. Among dietary intake, energy had significant positive correlation carbohydrate intake and fat intake only for females.

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Table 1: General descriptive statistics (males and females).

	N		Minimum		Maximum		Mean		Std. Deviation	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Age	27	26	14	14	23	24	18.70	17.62	2.785	2.83
Years in games	27	26	1	1	4	5	2.15	3.00	.989	1.23
Height(cm)	27	26	158.90	140.80	185.80	170.70	173.24	157.97	5.38	6.64
Weight (Kg)	27	26	47.00	37.00	71.00	60.10	58.874	48.04	7.32	6.04
Triceps skinfold (mm)	27	26	2.2	2.8	5.4	5.6	4.2	4.6	0.62	0.58
Biceps skinfold (mm)	27	26	2.6	3.00	5.8	6.00	4.63	5.02	1.02	1.33
Subscapular skinfold (mm)	27	26	6.8	8.2	13.2	14.4	8.95	10.24	2.23	2.34
Suprailiac skinfold (mm)	27	26	6.2	6.8	10.2	11.4	8.81	9.02	3.02	3.33

Table 2: Descriptive statistics for anthropometric parameters and VO2 max (males and females).

	N		Minimum		Maximum		Mean		Std. Deviation	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
BMI (kg/m^2)	27	26	16.46	15.97	23.72	23.13	19.60	19.23	2.14	1.89
Sum of Skin Fold (mm)	27	26	16.60	14.50	25.00	23.20	20.34	19.04	2.30	1.97
Fat %	27	26	6.44	8.55	15.58	16.40	10.55	11.62	2.66	2.40
Fat free mass %	27	26	84.42	83.60	93.56	91.45	89.45	88.38	2.66	2.40
VO2 max (ml/kg/min)	27	26	41.80	35.10	72.69	69.26	56.08	46.96	7.78	6.58

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Table 3: Descriptive statistics for dietary intake (n = 53).

	N	Minimum	Maximum	Mean	Std. Deviation
Energy (kcal)/day	53	1442.64	2812.00	2104.23	312.80
Carbohydrate (gm.) /day	53	226.50	616.00	470.58	88.75
Fat (gm.) /day	53	33.70	834.30	123.15	107.67
Protein (gm.) /day	53	41.00	117.00	76.57	19.41
Calcium (mg) /day	53	337.00	1444.20	692.29	204.01
Iron (mg) /day	53	4.30	50.30	25.59	11.17
Percentage Adequacy for Energy Intake	53	51.52 %	120.69 %	83.1%	14.34
Percentage Adequacy for Carbohydrate	53	40.74 %	116.67 %	86 %	16.64
Percentage Adequacy for Fat	53	112.33 %	481.00 %	364.39 %	359.61
Percentage Adequacy for Protein	53	68.33 %	195.00 %	135.64 %	34.65
Percentage Adequacy for Calcium	53	44.25 %	180.53 %	100.66 %	30.3
Percentage Adequacy for Iron	53	13.44 %	295.88 %	114.84 %	55.66

Relationship between dietary intake and body composition

Energy intake had significant positive correlation with BMI, SSF (only males), fat %, and negative correlation with FFM. Carbohydrate intake was positively correlated with fat % and negatively with FFM. Likewise, significant positive associations of fat intake were found with BMI andSSF for the group as a whole and association of fat intake specifically in females was found to be positive with fat % and negative with FFM ($p < 0.05$).

Relationship between dietary intake and VO2 max

VO2 max had significant positive correlation with protein, calcium and iron intake. A negative non-significant association was also found with carbohydrate and fat intake.

Relationship between body composition and VO2 max

VO2 max didn't share any significant association with any body composition measure in this study, however certain weak and non-significant associations were observed with SSF in males and with fat% and FFM for the group as a whole.

The associated variables were further analyzed for linear relationship with the help of scatter plots (figure 2). Linear regression and prediction equations were formed for variables showing a linear trend (tables 8 and 9).

It can be seen from the table above that in males a variation in total daily energy intake and carbohydrate intake explains the 58.7%[a] and 58.9%[b] variation in overall body fat % respectively. Total daily protein intake explains 30.2%[c] variation in the VO2 max.While, in females the variation in daily calcium intake explains only 19.6% variation in VO2 max. No linear relationship was found when the analysis for both males and females was done together.

Discussion

Dietary pattern of Indian long-distance runners

This study assessed the variation in the dietary pattern of Indian long-distance runners against recent ICMR norms. Figure 1 shows that Indian long-distance runners did not meet up the daily requirement of total energy intake and carbohydrate. However, consumption of

Table 4: Descriptive statistics for dietary intake (males and females).

	N		Minimum		Maximum		Mean		Std. Deviation	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Energy (kcal)/day	27	26	1442.64	1565.00	2807.00	2812.00	2125.55	2082.09	344.14	281.7
Carbohydrate (gm.)/day	27	26	226.50	321.00	595.00	616.00	456.76	484.92	97.64	77.77
Protein (gm.)/day	27	26	41.00	51.00	117.00	102.30	76.52	76.62	22.98	15.32
Fat (gm.)/day	27	26	33.70	56.00	834.30	235.00	141.82	103.78	144.78	39.33
Calcium (mg)/day	27	26	546.00	337.00	1444.20	892.00	805.56	574.66	184.36	151.59
Iron (mg)/day	27	26	4.30	6.00	50.30	45.00	25.61	25.57	11.39	11.18
Percentage Adequacy for Energy Intake	27	26	51.52%	70.18%	102.82 %	120.69%	75.83%	90.67%	12.62	12.05
Percentage Adequacy for Carbohydrate	27	26	40.74%	60.80%	105.76 %	116.67%	81.93%	90.23%	17.76	14.54
Percentage Adequacy for Protein	27	26	68.33%	98.08%	195.00%	186.00%	128.45%	143.11%	38.61	28.85
Percentage Adequacy for Fat	27	26	112.33%	140.00%	781.00%	587.50%	402.65%	324.65%	491.7	119.66
Percentage Adequacy for Calcium	27	26	75.00%	44.25%	180.53%	142.17%	119.2%	101.42%	24.61	22.86
Percentage Adequacy for Iron	27	26	13.44%	23.08%	295.88%	214.29%	122.2%	107.19 %	61.26	49.22

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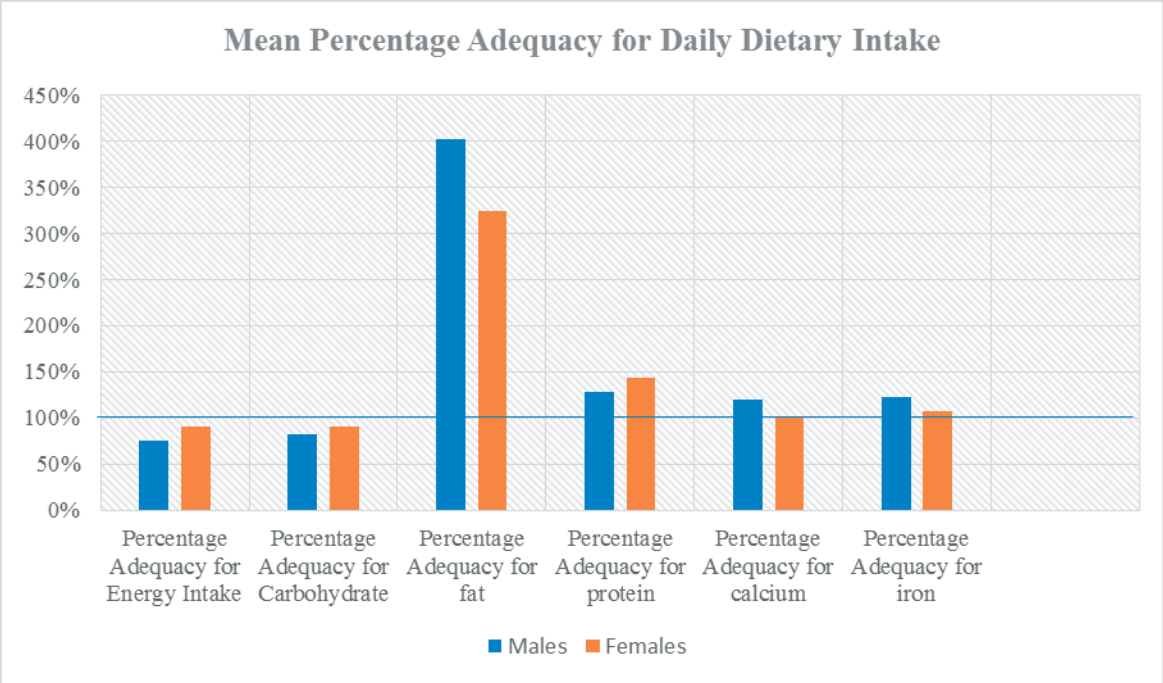

Figure 1: Percentage Adequacy for dietary intake in males and females.

protein, calcium, and iron was found to be above optimum. Fat consumption was found to be considerably high among the group. The interview during dietary recall reflected the trend of high fat low carbohydrate diet among Indian players [7–8, 10].The reasons behind such a trend can be attributed to their accustomed eating behavior as most of the players were from the northern part of the country, where consumption of buffalo's milk loaded with high fat content, homemade butter, *desi ghee* (clarified butter extracted from cow or buffalo's milk) and other saturated fats is a part of their culture. Also, the group mainly consisted of players belonging to late adolescence, the age when youth becomes prey of unhealthy nutritional behaviors and athletes are no exception to that [14]. However, it can be argued that high fat low carbohydrate diet results in metabolic adaptations which enhances oxidation of fat during long distance running when availability of carbohydrate is low [15].

Effect of dietary pattern on body composition

Number of calories consumed and the relative distribution of various nutrients in diet directly affect body mass and composition [16–18]. Tables 6-8 show that BMI is related to daily energy intake and fat intake, skinfolds were related to fat intake and fat% was related to daily energy and carbohydrate intake in both males and females ($p < 0.05$). Additionally, fat intake has been found to be associated with fat% in females (table 8, $p < 0.05$). An increase in energy intake leads to a linear increase in fat% of male players and more than half of the variation in fat content can be explained by the daily energy intake ($R^2 = 0.587$). Aforementioned relationship of body composition parameters with total energy intake, dietary carbohydrate, and fat intake favor the fact that these macronutrients can contribute to a negative energy balance to achieve a lean and slender athletic body for long distance running [19]. BMI and skinfolds are interchangeably used methods of estimating relative obesity and adiposity as reported by various studies [17, 18]. Present study also suggests the association of BMI and skinfolds with obesity and body composition.

Carbohydrates are needed as substrates for metabolic pathways leading to glycogen synthesis which is essential for improved endurance and effective recovery [15]. However, carbohydrates of moderate to high glycemic index are recommended for athletes. Meanwhile, the present study suggests

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Table 5: Pearson's correlation coefficient for variables under study (n = 53).

	Weight (Kg)	BMI (kg/m²)	Sum of skinfolds (cm)	Fat %	Fat free mass	VO2max (ml/kg/min)	Energy (Kcal/day)	Carbs (gm/day)	Protein (gm/day)	Fat (gm/day)	Calcium (mg/day)	Iron (mg/day)
Weight (kg)	1	.682**	.417**	.090	–.090	.275	.203	.046	.219	.277*	.414	.216
BMI (kg/m²)		1	.440*	.388**	–.388**	.018	.333*	.198	.221	.315*	.037	.374
Sum of skinfolds (cm)			1	.330*	–.330*	.100	.344	.131	.110	.325*	.166	.040
Fat %				1	–1.000**	–.213	.556**	.585**	.125	.108	-.078	.230
Fat free mass					1	.213	–.556**	-.585**	-.125	–.108	.078	–.230
VO2max (ml/kg/min)						1	.266	-.115	.532**	.283	.631**	.367*
Energy (Kcal)/ day							1	.729**	.082	.365	.148	.019

**Correlation is significant at the 0.01 level (2-tailed).
*Correlation is significant at the 0.05 level (2-tailed).

Table 6: Pearson's correlation coefficient for variables under study (males, n = 27).

	Weight (Kg)	BMI (kg/m²)	Sum of skinfolds (cm)	Fat %	Fat free mass	VO2 max (ml/kg/min)	Energy (Kcal/day)	Carbs (gm/day)	Protein (gm/day)	Fat (gm/day)	Calcium (mg/day)	Iron (mg/day)
Weight (kg)	1	.866**	.201*	.257	–.257	.015	.294	.230	.237	.351*	.142	.388
BMI (kg/m²)		1	.365*	.327*	–.327*	.078	.361*	.245	.256	.399*	.009	.386
Sum of skinfolds (cm)			1	.531**	–.531**	–.072	.491**	.327	.003	.439*	–.031	.069
Fat %				1	–1.000**	–.050	.766**	.778**	.247	.163	.006	.098
Fat free mass					1	.050	–.766**	–.778**	–.247	–.163	–.006	–.098
VO2max (ml/kg/min)						1	.209	.097	.550**	.246	.483*	.383*
Energy (Kcal)/day							1	.796	.132	.370	–.026	.024

**Correlation is significant at the 0.01 level (2-tailed).
*Correlation is significant at the 0.05 level (2-tailed).

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Table 7: Pearson's correlation coefficient for variables under study (females, n = 27).

	Weight (Kg)	BMI (kg/m²)	Sum of skinfolds (cm)	Fat %	Fat free mass	VO2max (ml/kg/min)	Energy (Kcal/day)	Carbs (gm/day)	Protein (gm/day)	Fat (gm/day)	Calcium (mg/day)	Iron (mg/day)
Weight (kg)	1	729**	472*	.350	–.350	.285	.070	.134	.382	.297	–.010	.139
BMI (kg/m²)		1	.528**	.539**	–.539**	.202	.283**	.177	.169	.275**	–.061	.365
Sum of skinfolds (cm)			1	.272**	–.272**	.080	.113	.019	.324	.215	.034	.006
Fat %				1	–1.000**	–.219	.331**	.275**	–.077	.291**	.115	.397
Fat free mass					1	.219	–.331**	–.275**	.077	–.291**	–.115	–.397
VO2max (ml/kg/min)						1	.368	.236	.449**	.258	.443*	.425**
Energy (Kcal)/day							1	.680**	–.011	.499**	.375	.011

**Correlation is significant at the 0.01 level (2-tailed).
*Correlation is significant at the 0.05 level (2-tailed).

Table 8: Regression analysis for variables having linear relationship (males and females).

S.No.	Dependent Variable (y)	Independent Variable (x)	Simple Correlation(R)	Coefficient of Determination(R^2)	Constant (a)	Slope (β)	Significance (p)
1.	Fat% (males)	Energy (kcal)/day	0.766	0.587[a]	–2.058	0.006	0.00
2.	Fat% (males)	Carbohydrate (g)/day	0.778	0.589[b]	0.861	0.021	0.00
3.	VO2 max (ml/kg/min) (males)	Protein (g)/day	0.550	0.302[c]	41.849	0.186	0.00
4.	VO2 max (ml/kg/min) (females)	Calcium (g)/day	0.443	0.196	35.917	0.019	0.02

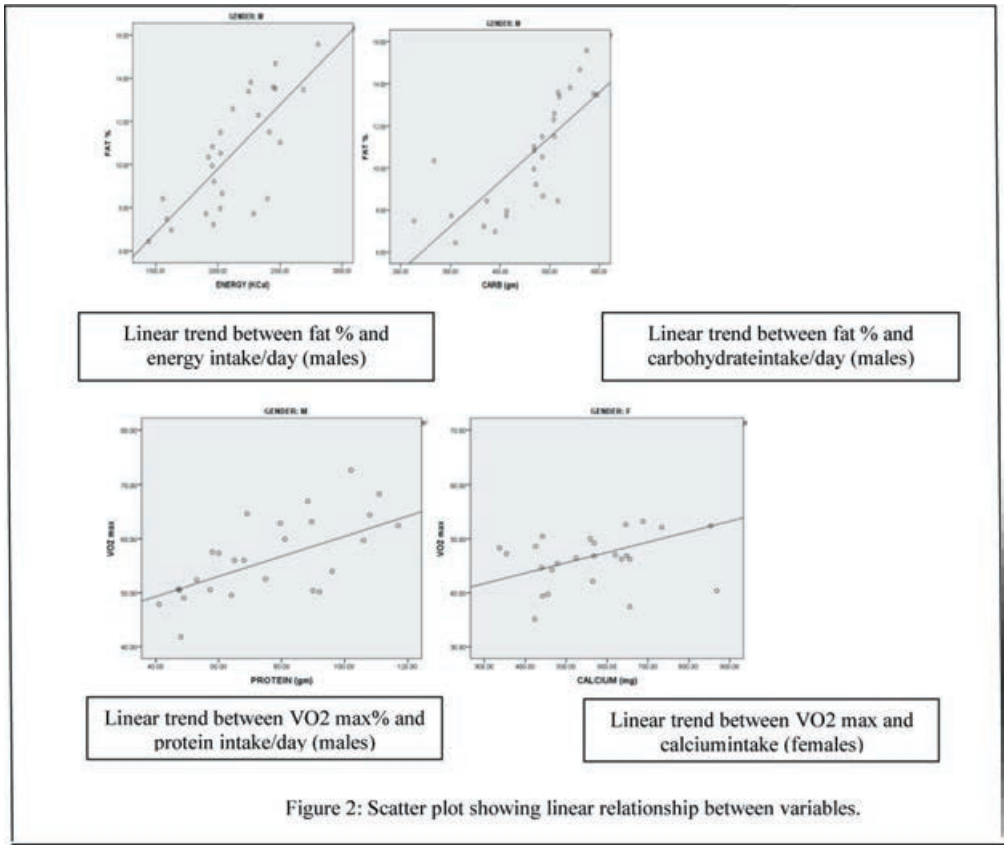
Linear trend between fat % and energy intake/day (males)
Linear trend between fat % and carbohydrateintake/day (males)
Linear trend between VO2 max% and protein intake/day (males)
Linear trend between VO2 max and calciumintake (females)
Figure 2: Scatter plot showing linear relationship between variables.

Figure 2: Scatter plot showing linear relationship between variables.

that undesirable carbohydrate intake can lead to an increase in fat content in the body [$R^2 = 0.589$].

Effect of dietary pattern on performance

Studies are there on dietary pattern, body composition, and performance of Indian athletes [7]. However, no study has been done to study the impact of dietary pattern on VO2 max of Indian long-distance runners. The results of the study suggest a linear relationship of VO2 max with protein, iron, and calcium but not with other nutritional components.

Table 9: Prediction equations.

S. No.	Prediction equations $y = a + \beta x$
1.	Fat%= –2.058+0.006 [Energy (kcal)] **(males)**
2.	Fat%= 0.861+0.021 [Carbohydrate (g)] **(males)**
3.	VO2 max (ml/kg/min) = 41.849+0.186 [Protein (g)] **(males)**
4.	VO2 max (ml/kg/min) = 35.917+0.019 [Calcium (mg)] **(females)**

Protein

Protein is considered as a key element of athletic success and players consume it in their diet as well as in supplements. Endurance athletes require it to maintain lean body mass, muscle repair, and synthesis of mitochondrial enzymes for muscle protein metabolism [15]. The findings of the study don't support a large explanation of variation in the VO2 max caused due to protein levels in diet ($r=0.550$, $R^2=0.302$, $p<0.01$).

Iron

Iron requirement of athletes is more than that of the sedentary population reaching up to even 70% above the recommended daily allowance [15, 16]. The reason behind it can be that long-distance runners suffer from iron deficiency anemia (IDA). A phenomenon called foot

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strike hemolysis occurs in which RBCs keep on getting ruptured when long distance runners hit the track during running [16]. Also, in general terms iron has been known as a carrier of oxygen and running players require continuous and elevated supply of oxygen for a long duration. However, iron consumption alone doesn't contribute much to variation in VO2 max.

Calcium

Calcium has been reported to be associated with VO2 max and bone mineral density [20], however, the exact mechanism is not known. A similar trend has also been observed in the current study ($r = 0.443$, $R^2 = 0.196$, $p < 0.01$).

Role of total energy intake, carbohydrate, and fat intake

Energy balance is a determining factor for athletic performance. An excess of calories leads to undesirable weight and fat gain and a deficit in energy leads to fatigue, injuries, delayed recovery, and muscle loss. Carbohydrates are required for maintenance of glycogen stores in the muscles. Any unfavorable change in glycogen levels can negatively impact muscle strength, aerobic, and anaerobic components of athletic performance. The lipid component in diet helps in maintenance of cell membrane integrity and in the absorption of liposoluble vitamins required in synthesis of various hormones involved in vital body functions [21]. Though, during specific training phases such as just before competition it is advisable to cut down calories coming from carbohydrates and fats.

Significant difference was found between males and females in terms of sum of skinfolds, VO2 max, and calcium intake. Higher sum of skinfolds in females under study is consistent with the findings of other studies reporting such observations in general due to hormonal differences [22]. Males possess a higher oxygen carrying capacity due to lesser body fat than females- another gender specific physiological difference like maximum heart rate, stroke volume, etc [22]. Consumption of calcium among female runners is higher to combat low bone mineral density due to estrogen dominance in females and altered menstrual cycle resulting out of strenuous physical training [23].

Conclusion

Dietary intake has an impact on both body composition and VO2 max (performance). Good diet is important for training, to fight against diseases, and to recover fast from fatigue and injuries. Availability of substrates for proper functioning of metabolic pathways requires an adequate distribution of nutrients in diet. Nutritional recommendations derived from latest scientific knowledge on peculiarities of each sport and phase of training do exist but have not been incorporated by trainers as part of athletic development. It is highly recommended to conduct similar grass root level studies on Indian athletes to identify their nutritional requirements based upon the sporting discipline they belong to and phases of training they undergo.

Conflict of Interest

The authors declare no conflict of interest.

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Original Research

Association between night eating syndrome in overweight and obese children 10-17 years of age and dyslipidemia

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Abstract

Background and Aims: Night eating syndrome **(**NES) is one of the reasons for increased prevalence of obesity. Nevertheless, there is lack of knowledge about the influence of NES on lipid metabolism in children. The objective of the study was to determine the influence of NES on the lipid profile in overweight and obese children 10–17 years of age. **Material and Method:** A population of 110 children with excess weight and obesity was enrolled in the study. NES was diagnosed based on existing criteria. Anthropometric measurements were performed for all participants. Lipid profile assessments included detection of TC, HDL-C, and TG with an enzymatic method and formula assessment for LDL-C, VLDL-C, and non-HDL-C levels. **Results:** NES was diagnosed in 21.82% of children. Dyslipidemia was detected in 70.83% of children with NES and in 44.19% subjects in the group without NES ($p = 0.04$). Atherogenic level of HDL-C was diagnosed in 45.83% subjects with NES compared with children without NES 15.12% ($p = 0.001$). Multivariate regression analysis has found significant association between NES and evidence of dyslipidemia and HDL-C level in the population of obese and overweight children ($p < 0.05$). **Conclusions:** NES is one of the reasons for changes in lipid profile in children; therefore, screening for eating disorders in overweight and obese children must be implemented in routine practice to reduce the risk of dyslipidemia and its consequences.

Keywords: children, lipids, night eating syndrome, obesity.

Background and Aims

Night eating syndrome (NES), as a type of eating disorder, has been studied for more than 60 years among different weight groups [1]. NES is characterized by abnormal timing of food intake, which could be accompanied by changes in sleep patterns [1]. NES was found to be genetically determined; the chances of having such type of eating disorder are 5 times higher in children who have relatives with the same problem [1, 2, 3]. The prevalence of NES varies. It depends on the age and the weight of the patient, and his socioeconomic status [3]. Nevertheless, the exact cause is still unknown. It is also unknown what is primary, i.e., whether NES causes obesity or obesity causes NES [1, 3]. Notably, eating disorders in children and adolescents are difficult to recognize and diagnose; many of them can be described as Eating Disorders Not Otherwise Specified [4]. Despite extensive research on the subject, the problem of NES as a type of eating disorder in pediatric population is still ambiguous and debatable.

It should be emphasized, that both NES and lipid metabolism has circadian patterns [5]. Disturbances of the rhythm of daily activity causes failure of circadian rhythm, which is associated with the occurrence of metabolic syndrome, components of which are abdominal type of obesity and dyslipidemia [6]. Night eating and sleep disorders as the components of NES could lead to changes in circadian secretion of melatonin

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and leptin and, as a result, all disturbances in metabolic activity [5]. Notably, lipids make up 80% from 15% of all metabolites with circadian rhythm [5]. At the same time, it should be emphasized that the diurnal metabolic rhythms are influenced not only by internal factors, but also by a number of external factors, in particular, exposure to light at night, duration and quality of sleep, food intake and physical activity [2, 5].

Therefore, NES could be a potential risk factor of metabolic disorders. The influence of eating disorders on the lipid profile has been studied in adult population while pediatric subjects were not taken into account [7]. However, studies on dyslipidemia and NES are still lacking. This is why the research community is deeply interested in dyslipidemia and its connections with eating disorders. Quite recently, manifestations of this problem in children have received considerable attention. Therefore, it has become the topic of our research.

The aim of the study was to determine the impact of NES on lipid metabolism in overweight and obese children 10–17 years of age.

Material and Method

Study design and patients

A population of 90 obese (81.82%) and 20 overweight (18.18%) children, 10–17 years of age, was recruited by the study. All children were assessed in Ternopil Regional Hospital, Ukraine. Informed consent was obtained from each child's legal representative(s). The study protocol conformed to the ethical guidelines of Helsinki's Declaration and was approved by the Bioethics Commission of I. HorbachevskyTernopil State Medical University (Protocol 24, dated 27.08.2014).

Laboratory, anthropometric and clinical data collection

Physical examination was performed in all study subjects: weight, height, waist circumferences (WC), and hip circumferences (HC) were measured in internationally accepted units (kg, m). Body mass index (BMI) and waist/hip ratio (W/H ratio) were also calculated.

The diagnosis of NES was based on the following criteria [8, 9]:

1. Increased food intake in the evening and/or at night, which was manifest by one or both of the following: a) at least 25% of the total amount of food consumed after the evening meal; b) at least two episodes of food intake at night per week.
2. Being aware of eating too late.
3. At least three of the following characteristics should be present: a) lack of appetite in the morning and/or skipping breakfast four or more times during a week; b) a strong craving for food between dinner and bedtime and/or during the night; c) presence of a sleep disorder (trouble falling asleep and/or episodes of insomnia) on four or more nights per week; d) believing/feeling like one should eat before going to bed; e) presence of depression and/or low mood in the evening.
4. Presence of an eating disorder associated with significant distress and/or impaired body function.
5. Minimal duration of disrupted eating patterns of three months.
6. Presence of an eating disorder unrelated to certain medical disorders, abuse, or dependence on taking psychoactive substances, the effects of certain medications, and mental disorders.

Total cholesterol (TC), high density lipoprotein (HDL-C), and triglycerides (TG) were determined in the serum using an enzyme method (reagents "Human GmbH", Germany). The following formulas were used to find the levels of low density lipoprotein cholesterol (LDL-C), very low density lipoprotein (VLDL-C), and non-HDL-cholesterol (non-HDL-C):

$$\text{LDL-C (mmol/l)} = \text{TC(mmol/l)} - (\text{TG(mmol/l)}/2.2 + \text{HDL-C[mmol/l]});$$
$$\text{VLDL-C (mmol/l)} = \text{TG(mmol/l)}/2.2;$$
$$\text{non-HDL-C (mmol/l)} = \text{TC(mmol/l)} - \text{HDL-C (mmol/l)}.$$

According to expert recommendation, acceptable, borderline, and high/low (for

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HDL-C) levels of lipids have been identified [10]. The following lipid profile parameters were seen as acceptable lipid levels: total cholesterol (TC) lower than 4.40 mmol/l (170 mg/dl), low density lipoproteins (LDL-C) less than 2.85 mmol/l (110 mg/dL), non-HDL-C lower than 3.11 mmol/l (120 mg/dL), triglycerides lower than 1.0 mmol/l (90 mg/dL), high density lipoproteins (HDL-C) higher than 1.17 mmol/l (45 mg/dL). The following values were seen as borderline: TC: 4.40—5.17 mmol/l (170–199 mg/dL); LDL-C: 2.85–3.36 mmol/l (110–129 mg/dL); non-HDL-C: 3.11-3.75 mmol/l (120-144 mg/dL); triglycerides: 1.02–1.46 mmol/l (90–129 mg/dL); HDL-C: 1.04—1.17 mmol/l (40—45 mg/dL). The levels of lipids equal to or higher than 5.18 mmol/l (200 mg/dL) for TC, 3.37 mmol/l (130 mg/dL) for LDL-C, 3.76 mmol/l (145 mg/dL) for non- HDL-C, 1.47 mmol/l (130 mg/dL) for triglycerides and lower than 1.04 mmol/l (40 mg/dL) for HDL-C were regarded as atherogenic and dyslipidemia was diagnosed.

Statistical analysis

Data management and analysis was performed using STATISTICA 7.0 software. Comparison of two independent samples with normal distribution was carried out using Student's t-test; Mann-Whitney U-test was used for parameters with abnormal distribution. The differences were considered significant at $p < 0.05$. Two-tailed Fisher exact test and Pearson Chi-square test were used to analyze the frequency tables. Odds ratio (OR) and its 95% confidence interval (95% CI) were calculated to evaluate the impact of the factor on the outcome. Logistic regression was performed to find the association between NES and parameters of lipid metabolism.

Results

Night-eating syndrome was diagnosed in 24 children (21.82 % [95% CI 13.98; 32.46]). There were no gender-specific differences concerning the frequency of NES: the disorder was found in 17.65% (95% CI 9.88; 29.11) boys and in 36% girls (95% CI 16.46; 68.34) (Fisher exact test, two-tailed $p = 0.06$): the male/female ratio in the NES group was 1.67/1 (62.50% and 37.50%, respectively).

Socio-demographic and clinical characteristics of children recruited in the study are presented in Table 1. Anthropometric parameters (body weight, BMI, WC, HC) were significantly higher in group of children with NES (table 1) (Student's t-test, $p < 0.05$), despite absence in morbidity rate (overweight/obesity) in the compared groups (Fisher exact test, two-tailed $p > 0.05$). The prevalence of NES was 20% (95% CI 5.45; 51.21) among overweight children and 22.22% (95% CI 13.57; 34.32) among their peers with obesity (Fisher exact test, two-tailed $p = 0.99$). Taking into account that WC was significantly higher among night eaters, we have investigated the impact of NES on abdominal obesity. In the group with NES, AO was found in 75.00% of children versus 83.72% in the non-NES group (Fisher exact test, two-tailed, $p = 0.37$).

Dyslipidemia was diagnosed in 70.83% of children with NES (95% CI 41.26; 100.00) and in 44.19% subjects in the group without NES (95% CI 31.27; 60.65): Fisher exact, two-tailed, $p = 0.04$; OR = 3.07; 95% CI 1.15–8.15; $p = 0.02$ (NES = exposure, dyslipidemia = outcome) (table 2).Among serum lipid levels only HDL-C has significant differences across the groups with and without NES (table 2). It should be emphasized that HDL-C levels were higher in the group without NES: 1.25 (1.14; 1.38) versus 1.10 (0.98; 1.31) in the group of subjects diagnosed with NES ($p = 0.01$ for Mann-Whitney U test).

Analysis of serum lipid levels depending on cardiovascular risk has shown that levels of TC, LDL-C, non-HDL-C and TG were not significantly different across the groups with and without NES ($p > 0.05$ for Pearson Chi-square test) (table 3). Nevertheless, acceptable levels of HDL-C were registered in 33.33% of children with NES (95% CI 14.39; 65.68) and in 68.60% of subjects without NES (95% CI 52.23; 88.49) ($p = 0.001$). A reverse pattern was found for low level of HDL-C: it was diagnosed in 45.83% subjects in the group with NES (95% CI 22.88; 82.01); in the group without NES low levels of HDL-C were detected less often: in 15.12% of children (95% CI 8.05; 25.85) ($p = 0.001$). There were no statistical differences in borderline levels of HDL-C (table 3). The

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Table 1: Socio-demographic and clinical variables of overweight and obese children, 10-17 years of age, depending on the presence of night eating syndrome.

Parameters		Groups		P
		NES(+)	NES(–)	
age, years		16.17 ± 0.64	14.98 ± 1.68	0.002*
gender	boys	15 (17.65%)	71 (82.35%)	0.060
	girls	9 (36.00%)	17 (64.00)	
weight status	overweight	4 (20.00 %)	16 (80.00%)	0.999
	obesity	20 (22.22%)	70 (77.78)	
Weight, kg		99.63 ± 23.17	89.31 ± 15.63	0.012*
Height, m		1.72 ± 0.10	1.72 ± 0.11	0.932
BMI, kg/m^2		33.54 ± 5.84	30.02 ± 3.27	<0.001*
WC, cm		102.83 ± 13.63	96.41 ± 9.37	0.009*
HC, cm		111.06 ± 11.20	106.73 ± 6.59	0.020*
W/H ratio		0.93 ± 0.07	0.90 ± 0.05	0.068

NOTES. NES+ - group of children with diagnosed NES; NES- - group of children without NES, BMI – body mass index; WC – waist circumference; HC – hip circumference; W/H ratio – waist/hip ratio;
* = statistically significant results.

Table 2: Lipid profile in children 10–17 years of age depending on the presence of night eating syndrome (Me [Q25; Q75]).

Indices (mmol/l)	Groups		Mann-Whitney U test, p
	NES(+)	NES(–)	
Total cholesterol	3.90 (3.42; 4.97)	4.08 (3.41; 4.52)	0.93
LDL-cholesterol	2.29 (1.76; 2.94)	2.13 (1.65; 2.71)	0.36
VLDL-cholesterol	0.47 (0.36; 0.66)	0.52 (0.41; 0.70)	0.20
Non-HDL cholesterol	2.80 (2.24; 3.69)	2.71 (2.15; 3.25)	0.43
Triglycerides	1.03 (0.79; 1.52)	1.17 (0.90; 1.55)	0.20
HDL cholesterol	1.10 (0.98; 1.31)	1.25 (1.14; 1.38)	0.01*

NOTES. NES(+) - group of children with diagnosed NES; NES(-) - group of children without NES
* = statistically significant results.

calculation of odds ratio has shown that NES may influence HDL-C levels. For low HDL-C levels, the following values were obtained: OR = 4.75; 95% CI 1.75–12.87 and p = 0.002. For acceptable HDL-C levels, the following values were obtained: OR = 0.23; 95% CI 0.09–0.60 and p = 0.003. For borderline HDL-C levels, the following values were obtained: OR = 1.35; 95% CI 0.43–4.23 and p = 0.602.

One of the NES criteria is the time of last food intake before going to sleep. Therefore, we have analyzed the influence of time between last food intake and bedtime and parameters of lipid status. Our study has found that HDL-C levels were closely related to the time of food intake before going to sleep (r = 0.20; p = 0.04) (table 4).

Results of regression analysis (univariate and multivariate [after adjustment for weight status]) have confirmed association between NES and evidence of dyslipidemia in the population of obese and overweight children: AOR = 3.09; 95 %

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Table 3: Serum lipid levels depending on the presence of night eating syndrome.

Indices	NES +		NES –		p-value
	n	%	n	%	
Dyslipidemia	17	70.83	38	44.19	0.04*
Total cholesterol					
Acceptable	16	66.67	61	70.93	0.47
Borderline	3	12.50	15	17.44	
High	5	20.83	10	11.63	
LDL-cholesterol					
Acceptable	17	70.83	66	76.74	0.83
Borderline	4	16.67	11	12.79	
High	3	12.50	9	10.47	
Non-HDL cholesterol					
Acceptable	13	54.17	57	66.28	0.46
Borderline	5	20.83	16	18.60	
High	6	25.00	13	15.12	
Triglycerides					
Acceptable	12	50.00	33	38.37	0.35
Borderline	4	16.67	27	31.40	
High	8	33.33	26	30.23	
HDL-cholesterol					
Acceptable	8	33.33	59	68.60	0.01*
Borderline	5	20.83	14	16.28	
Low	11	45.83	13	15.12	

Notes. * – statistically significant result.

Table 4: The correlation between last food intake before going to bed and serum lipid levels in groups with and without night eating syndrome.

Parameters	Total (n = 110)	
	Spearman, r	*p*-value
Total cholesterol	0.12	0.20
LDL cholesterol	0.08	0.41
VLDL cholesterol	0.05	0.59
Non-HDL cholesterol	0.08	0.40
Triglycerides	0.05	0.60
HDL cholesterol	0.20	0.04*

NOTES. * – statistically significant result.

CI 1.14–8.41 ($p < 0.05$). Among all lipids only HDL-C was significantly related to the presence of NES: AOR = 6.39; 95 % CI 2.06–19.87 ($p < 0.05$) (table 5).

Discussion

The data in the available literature highlights the impact of eating behaviors on obesity in children [11, 12]. It should be emphasized that many previous studies involved adult subjects of different age groups, sex, and ethnicity [13, 14]. The issue of NES in pediatric populations is a topic of ongoing discussion and research.

According to our results, the prevalence of NES was 21.82% (95% CI 13.98; 32.46), which is consistent with the data obtained by scholars in the US, where NES occurs at a rate of 6.5–21% among young individuals 9–19 years of age [14]. At the same time, as reported by investigators in the UK, this eating disorder occurs with a frequency of 8.9–14% among persons with obesity [9]. The latter differences in the prevalence of NES are

Table 5: Association between NES and parameters of lipidogram.

Indices	Univariate regression analysis			Multivariate regression analysis		
	unadjusted OR	95% CI	p	adjusted OR	95% CI	*p*
Dyslipidemia (presence/absence)	3.07	1.14–8.25	0.027*	3.09	1.14–8.41	0.027*
TC (high/acceptable)	0.52	0.15–1.78	0.297	0.53	0.16–1.80	0.305
LDL-C (high/acceptable)	0.77	0.18–3.22	0.594	0.81	0.19–3.46	0.773
non-HDL cholesterol (high/acceptable)	0.49	0.16–1.56	0.227	0.50	0.16–1.59	0.236
TG (high/acceptable)	1.05	0.36–3.03	0.925	1.05	0.36–3.04	0.925
HDL-C (low/acceptable)	6.24	2.06–18.86	0.001*	6.39	2.06–19.87	0.002*

NOTES: adjusted OR was calculated after adjustment for weight status (overweight/obesity).
* – statistically significant result.

attributable to the lack of representativeness of the samples selected for the study. In particular, this reflects the different age demographics of study subjects, as well as the differences in nutrition habits and food cultures in people of different national and ethnic backgrounds [14]. In addition, some scientists exclude children under the age of 13 years from evaluation for NES because the diet of children in this age group is mostly defined and controlled by their parents [14].

The results of our study have not found any gender differences concerning NES. Nevertheless, the literature reports that eating disorders are more typical for girls compared with boys; their frequency is 6 times higher in girls and three times higher in women [15, 16]. The absence of gender-specific differences concerning NES in our study can be explained by a small population of study subjects diagnosed with NES. Sex-dependent differences in eating behaviors are the result of hypothalamic-pituitary-gonadal axis function and the influence of other hormones and neuropeptides, such as ghrelin, cholecystokinin, glucagon-like peptide-1, glucagon, insulin, amylin, apolipoprotein A-IV, fatty-acid oxidation, leptin, serotonin, melanocyte stimulating hormone, neuropeptide Y, agouti-related peptide, melanin-concentrating hormone, and dopamine [16]. Both estrogens and androgens stimulate food intake: estrogens increase daily food intake through more frequent eating, while androgens increase meal sizes; the validity of these findings was supported by data obtained in gonadectomy [16].

In our study, NES was diagnosed in every fifth overweight child or child with obesity. The findings in this study are similar to the results obtained in an adult population study, where NES was considered a risk factor for obesity [9, 17, 18, 19]. However, studies by R.H. Striegel-Moore et al. and Calugi S. et al. negated the relationship between eating at night and being overweight in children [20, 21]. Such differences could be attributable not only to the different age, gender, and ethnic composition of study groups, but also to the time of assessment, because during the school vacation, which is typically three months long, the nutritional patterns of children change significantly [14, 18]. Other factors that could make a difference include dietary patterns in the families, as well as parental education and socio-economic status of the family [14, 18].

The data in literature suggests NES to be closely related to metabolic syndrome [19]. One of the core components of metabolic syndrome includes HDL-C levels. Similar findings were obtained in our study, i.e., the level of HDL-C was closely associated with NES in children 10–17 years of age. We have found children with NES to have a potential threefold increase in the risk of dyslipidemia compared to children without this eating disorder ($p = 0.02$). Other authors reported night snacking to increase TC and LDL-C levels [22]. This has been attributed to the changes in the circadian rhythm of cholesterol metabolism found in night eating. Changes in meal times impact the expression of cholesterol

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7-alpha-hydroxylase and 3-hydroxy-3-methylglutaryl-coenzyme Areductase, leading to hypercholesterolemia [22].

Previous researches have studied that cholesterol level and LDL-C have diurnal variations. In the same time data about circadian patterns of HDL-C level is still debatable; some of the studies deny this pattern, another has written about a very small-amplitude rhythm (2–4%) for HDL-C [5]. Notably, changes in food intake for several hours have significant effect on the cholesterol and leptin level [5].

Researches of the adult population emphasized that night work increased the risk of dyslipidemia, in particular, increased triglycerides level, free fatty acid level and decreased level HDL-C, which could be explained by changes in the circadian rhythm [23]. Noteworthy, sleep duration, obesity, and physical inactivity are the leading causes of dyslipidemia [5, 23].

In addition, it was found that having a meal before sleep contributes to decreasing in HDL-C level ($p < 0.05$). Recent studies have shown some advantages in eating at bedtime, in that it could help maintain protein synthesis and glycogen re-synthesis when a small, nutrient-dense and high-protein meal is taken in close connection with physical activity [24]. However, such circumstances are not typical for the examined cohort of children: the participants in our study were not healthy and physically active subjects; they were overweight or obese and typically had low level of physical activity, especially in evening and morning hours.

Lipid screening is recommended at the age of 9–11 years and at the age of 17–21 years (before and after puberty); nevertheless, if risk factors are present, selective screening may be performed [25]. That being said, the results of our study should be taken in the account when considering risk factors of dyslipidemia in children, which are not limited to obesity as a principal risk factor, but also include NES.

Conclusions

NES may have significant health implications in young people due to its contribution to excess weight or obesity and disorders of lipid metabolism. Our study has found NES to be one of the reasons for changes in the lipid profile in children; therefore, screening for eating disorders should be implemented as a routine practice to reduce the risk of dyslipidemia and the associated consequences.

Acknowledgments

Authors' contributions: All authors contributed to the study conception and design. Halyna Pavlyshyn designed the study, participated in discussion of the obtained results, revised and edited the paper. Kateryna Kozak provided the examination of the patients, data collection, analyzed the results. Mariya Marushchak participated in discussion of the obtained results, revised, and edited the paper. All authors read and approved the final manuscript.

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Conflict of Interest

The authors declare no conflict of interest.

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Original Research

Dietary intake and glutathione s-transferase (m1 and t1) variants in type 2 diabetes mellitus at USU hospital, Medan, Indonesia

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Abstract

Background and Aims: Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease caused by multifactorial, such as genetic and external factors, i.e. diet and lifestyle. This study aims to observe the differences of dietary intake T2DM patients in Universitas Sumatera Utara Hospital (USU) Hospital, Medan, Indonesia based on glutathione S-transferase M1 (GSTM1) and T1 (GSTT1) variants. **Material and Method:** This study was conducted on T2DM patients that were recruited at USU Hospital, Medan, Indonesia. Dietary intake was recorded by 24-hours food recall and analyzed with Nutrisurvey 2007. Multiplex PCR was performed to analyze GSTM1 and GSTT1 variants. **Results:** This study showed mean of lipid intake (g), Recommended Dietary Allowance (RDA) lipid (%), % lipid (%), and protein intake (g), RDA protein (%), % protein (%) in GSTM1 null were greater than GSTM1 positive (37.02 ± 2.77 vs 23.68 ± 4.3, $p < 0.05$; 53.6 ± 4.01 vs 34.2 ± 6.23, $p < 0.05$; 26.17 ± 1.22 vs 16.33 ± 2.23, $p < 0.05$; and 50.11 ± 3.64 vs 49.86 ± 11.79, $p > 0.05$; 83.3 ± 6.04 vs 82.94 ± 19.61, $p > 0.05$; 16.8 ± 0.69 vs 14.6 ± 1.37, $p > 0.05$). In GSTT1 gene, the mean of lipid intake (g), RDA lipid (%), % lipid (%) was greater in GSTT1 null than GSTT1 positive (33.32 ± 3.92 vs 32.66 ± 2.84, $p > 0.05$; 48.24 ± 5.68 vs 47.24 ± 4.12, $p > 0.05$; 23.69 ± 1.78 vs 22.81 ± 1.77, $p > 0.05$). **Conclusions:** Lipid intake, RDA lipid, % lipids, carbohydrate intake in GSTM1 positive and null or mean of energy intake in GSTT1 positive and null were significant differences in T2DM patients at USU Hospital, Medan, Indonesia.

Keywords: dietary intake, GSTM1, GSTT1, type 2 diabetes mellitus.

Background and Aims

Diabetes mellitus (DM) is a metabolic disorder associated with nutrients metabolism [1]. In 2017, the prevalence of DM was 451 million people (8.4%) in the world and it is estimated that in 2045 it will increase to 693 million people (9.9%) [2]. In 2030, people with DM are estimated to be 21.3 million in Indonesia [3]. Type 2 diabetes mellitus (T2DM) generally occurs in adults. T2DM is caused by insulin resistance and about 87% to 91% of all DM patients are estimated to be T2DM [1, 2].

Oxidative stress underlies the pathogenesis of T2DM. Oxidative stress in T2DM can cause complications such as neurodegenerative, cardiovascular disorders, etc. [4–6]. Oxidative stress can be overcome by antioxidants. One of the antioxidant groups that play a role in oxidative stress defense is endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione S-transferase (GST). GST is an antioxidant that fights against oxidative stress by detoxification of endogenous and exogenous electrophilic

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compounds, as well as metabolizing compounds formed from oxidative stress [7, 8].

The GST protein is synthesized based on genes encoded by predetermined nucleotide sequence. GST gene variations caused disturbance with the ability of GST enzymes in dealing with oxidative stress. Among the various types of GST, GSTM1 (Mu) and GSTT1 (Theta) are known to be polymorphic and widely studied in relation to susceptibility to disease [9].

Previous studies have shown an association between GSTM1 and GSTT1 gene variations with T2DM patients [10, 11]. The risk of suffering T2DM was related to external factors such as dietary intake. Previous studies showed differences of dietary intake in T2DM patients and healthy subjects. Dietary intake is an important determinant of insulin resistance as a pathogenesis of T2DM [12–14]. The association of dietary intake with T2DM has been known, and the relationship of GSTM1 and GSTT1 gene variations with T2DM has been widely studied, but the study about differences of dietary intake based on GSTM1 and GSTT1 variants in T2DM patients at USU Hospital has never been done.

Material and Method

Study design and patients

The cross-sectional study was carried out after obtaining approval from the Ethics Committee of Medical Faculty, Universitas Sumatera Utara (USU) EC No.116.KEPK FK USU-RSUP HAM in the year 2019. Fifty of T2DM patients recruited from endocrine polyclinic at USU Hospital according to PERKENI (Indonesian Endocrinology Association) guideline. All respondents were informed about the study protocol with written information and signed the informed consent.

Food recall and clinical data collection

Dietary intake was recorded using a 24-hour food recall questionnaire and using food model. Dietary intake data was analyzed by Nutrisurvey 2007. Examination of fasting blood glucose (FBG) was done after the patient underwent fasting for 8–12 hours the night before. Two hours post prandial blood glucose (2hPPG) were examined two hours after meal. Fasting blood glucose, 2hPPG and HbA1c tests were performed using Cobas 6000 analyzer with the principle of hexokinase and immunoturbidimetry (Roche Diagnostics, Switzerland) at USU Hospital Laboratory.

Genotyping GSTM1 and GSTT1 gene

Examination of GSTM1 and GSTT1 gene variants was carried out at Integrated Laboratory Medical Faculty of USU through several stages. DNA was isolated using DNA extraction kit (Promega, USA) and was extracted using buffy coat from peripheral leukocyte blood. DNA isolates measured the concentration and purity at 260/280 absorbents. DNA was stored at –80°C until further analysis.

Multiplex PCR method is performed to analyze genetic variation in GSTM1 and GSTT1. The primers were used for amplification showed in table 1. PCR reaction was 25 µL with the composition: 1 µL each primers forward and reverse, 12.5 µLTaq PCR master mix (Promega, US), 1 µL DNA sample, and nuclease free water add up to 25 µL. PCR was carried out with a pre-denaturation of 95°C for 5 minutes, denaturation of 94˚C for 30 seconds, primary anneling 63°C for 30 seconds, elongation 72˚C for 30 seconds. The amplification cycle was 35 cycles and post elongation was carried out at 72°C for 10 minutes.

The PCR products were analyzed by electrophoresis using 2% agarose (Invitrogen). The presence of DNA bands of PCR products was observed on the UltraViolet transluminator. The documentation showed that 215 bp fragment indicates GSTM1 variant and 480 bp fragment indicates GSTT1 variant with β-actin gene control at 92 bp [15].

Statistical analysis

Dietary intake data, GSTM1 and GSTT1 gene variations were analyzed using a statistical

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Table 1: Primers of GSTM1 and GSTT1.

Gene	Forward	Reverse
GSTM1	5′-GAACTCCCTGAAAAGCTAAAGC-3′	5′-GTTGGGCTCAAATATACGGTGG- 3′
GSTT1	5′-TTCCTTACTGGT CCTCACATCTC-3′	5′-TCACCGGATCATGGC CAGCA-3′
β-actin	5′-AATGTGAACATGTGGGACTTTGTG-3’	5′-CGCCAGTTCAGGACATTAGGAC-3′

program based on Windows computers with a significance level of 5% ($p < 0.05$). Differences of mean dietary intake levels were analyzed by Mann Whitney test.

Results

The characteristics of the study subjects were shown in table 2. Differences in characteristics and patterns of dietary intake based on GSTM1 and GSTT1 gene variants in T2DM patients can be seen in tables 3 and 4.

In this study population, out of fifty T2DM patients, 35 (70%) patients with GSTM1 null were found. There were differences in characteristics in each of these GSTM1 variant groups, but there were no statistically significant differences ($p > 0.05$). Dietary intake based on GSTM1 gene showed significant differences in mean lipid intake, RDA lipid, % lipid, % carbohydrate and vitamin E intake in GSTM1 positive compared to GSTM1 null ($p < 0.05$) (Table 3).

Table 2: Patients' characteristic.

Characteristic	Category	n (%)
Age (y.o)	<40	2 (4)
	41–50	10 (20)
	51–60	18 (36)
	61–70	14 (28)
	>70	6 (12)
Gender	Female	24 (48)
	Male	26 (52)
Duration of suffering DM	<5 years	29 (58)
	>5 years	21 (42)

From fifty T2DM patients in this study, GSTT1 positive were found in 27 subjects. Based on subject characteristics, there was an association of differences in levels of 2 h PPG between GSTT1 positive and GSTT1 null variants ($p < 0.05$), but there were none in FBG, HbA1c levels and duration of suffering DM. There were significant differences in the mean of energy, vitamin E and calcium intake between GSTT1 positive and GSTT1 null ($p < 0.05$), but not in other dietary intake (table 4).

Discussion

T2DM is a chronic metabolic disease caused by multifactorial reasons. Genetic variations are known to be associated with occurrence of T2DM, such as variations in the glutathione S-transferase (GST), GSTM1, and GSTT1 genes. In this study, the number of T2DM patients was greater in GSTM1 null than GSTM1 positive (70% vs. 30%) whereas GSTT1 positive was greater than GSTT1 null (54% vs. 46%). Previous studies have shown similar results where the distribution of GSTM1 null was greater than GSTM1 positive (62% vs. 38%), and GSTT1 positive was greater than GSTT1 null (65% vs. 35%) in T2DM patients in Egypt [11]. Different results from the T2DM study in Chinese population showed that GSTM1 positive was greater than GSTM1 null and GSTT1 null was greater than GSTT1 positive [16]. Study on T2DM patients in Iraq showed that both GSTM1 and GSTT1 null were greater than GSTM1 and GSTT1 positive [17]. The results of previous studies on T2DM patients showed that GSTM1 and GSTT1 positive were greater than GSTM1 and GSTT1 null in Brazil [10].

Genetic variations occur due to differences in the sequence of nucleotides between

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Table 3: Dietary intake and GSTM1 gene variant.

Characteristic and dietary intake	GSTM1		p value
	Positive (n = 15; 30%)	Null (n = 35; 70%)	
Fasting Glucose (mg/dL)	202.91 ± 32.22	232.66 ± 13.28	0.312
2hPPG (mg/dL)	285.94 ± 30.94	302.13 ± 15.19	0.601
HbA1c (%)	8.89 ± 0.61	8.99 ± 0.36	0.881
Duration of suffering DM (year)	8.73 ± 1.71	6.37 ± 1.03	0.229
Energy (kcal)	1355.04 ± 180.65	1303.4 ± 65.11	0.738
RDA Energy (%)	61.42 ± 8.78	60.25 ± 3.13	0.876
% Energy (%)	66.56 ± 8.87	63.94 ± 3.19	0.730
Lipid (g)	23.68 ± 4.3	37.02 ± 2.77	0.015*
RDA Lipid (%)	34.2 ± 6.23	53.6 ± 4.01	0.011*
% Lipid (%)	16.33 ± 2.23	26.17 ± 1.22	0.001*
Carbohydrate (g)	205.64 ± 25.74	170.2 ± 9.12	0.110
RDA Carbohydrate (%)	70.72 ± 8.85	58.56 ± 3.13	0.210
% Carbohydrate (%)	69.6 ± 3.4	57.02 ± 1.55	0.003*
Protein (g)	49.86 ± 11.79	50.11 ± 3.64	0.979
RDA Protein (%)	82.94 ± 19.61	83.3 ± 6.04	0.982
% Protein (%)	14.6 ± 1.37	16.8 ± 0.69	0.118
Vitamin C (mg)	15.4±2.92	13.04 ± 3.39	0.672
Vitamin E (mg)	16.41 ± 1.93	7.63 ± 3.54	0.006*
Kalsium (Ca) (mg)	385.52 ± 142.75	224.91 ± 73.22	0.409
Magnesium (Mg) (mg)	207.24 ± 74.17	187.54 ± 23.36	0.743
Besi (Fe) (mg)	5.67 ± 1.93	5.06 ± 0.56	0.689
Zinc (Zn) (mg)	5.12 ± 1.39	4.83 ± 0.34	0.788

Data are presented as mean ± standard deviation. p values: Mann-Whitney test

individuals that are related to race and ethnicity [18]. Genetic variations in GSTM1 and GSTT1 were known as factors of T2DM susceptibility. Previous studies have shown that GSTM1 and GSTT1 null decreased GST activity, thereby reducing the ability of this enzyme dealing with oxidative stress that arises in T2DM. Oxidative stress increases insulin resistance and worsens the disease [19, 20]. Genetic variation is not the only pathogenesis that caused people to suffer from T2DM. External factors also play an important role in the pathogenesis of T2DM. Genetic factors and their interactions with external factors such as dietary intake contribute to the development of T2DM. Heritability for T2DM is estimated around 26%. The interaction between genetic factors and dietary intake tends to be important, too [21–23].

In this study, significant differences were found in the mean energy intake in GSTT1 positive compared to GSTT1 null ($p < 0.05$), but there were not found in lipid, carbohydrate, and protein intakes. Energy is obtained from macronutrients such as carbohydrates, fats, and proteins. In order to be converted into energy, these nutrients undergo a metabolic process. Carbohydrate becomes glucose, fat becomes fatty acids, and protein becomes amino acids. Consumption of high carbohydrates and lipid food, in addition to low physical activity, will change the energy balance by storing energy as fat that is rarely used. This excessive macronutrients intake will

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Table 4: Dietary intake and GSTT1 gene variant.

Characteristic and dietary intake	GSTT1		p value
	Positive (n = 27; 54%)	Null (n = 23; 46%)	
Fasting Glucose (mg/dL)	197.78 ± 14.29	223.65 ± 21.53	0.337
2hPPG (mg/dL)	273.65 ± 16.91	305.4 ± 21.38	0.015*
HbA1c (%)	8.93 ± 0.43	8.98 ± 0.44	0.938
Duration of suffering DM (year)	7.37 ± 1.26	6.73 ± 1.27	0.729
Energy (kcal)	1363.05 ± 116.24	1267.05 ± 67.79	0.046*
RDA Energy (%)	62.21 ± 5.71	58.72 ± 3.09	0.612
% Energy (%)	66.87 ± 5.71	62.2 ± 3.32	0.503
Lipid (g)	32.66 ± 2.84	33.32 ± 3.92	0.897
RDA Lipid (%)	47.24 ± 4.12	48.24 ± 5.68	0.892
% Lipid (%)	22.81 ± 1.77	23.69 ± 1.78	0.730
Carbohydrate (g)	196.73 ± 16.84	173.9 ± 9.96	0.534
RDA Carbohydrate (%)	66.22 ± 5.79	59.84 ± 3.42	0.537
% Carbohydrate (%)	68.77 ± 2.46	59.65 ± 2.28	0.535
Protein (g)	51.74 ± 7.46	48.03 ± 3.35	0.671
RDA Protein (%)	86.05 ± 12.41	79.85 ± 5.55	0.669
% Protein ((%)	16.65 ± 0.89	15.7 ± 0.92	0.468
Vitamin C (mg)	14.7 ± 2.58	14.67 ± 4.62	0.995
Vitamin E (mg)	15.4 ± 3.47	11.86 ± 3.95	0.047*
Kalsium (Ca) (mg)	405.62 ± 128.89	117.52 ± 23.14	0.048*
Magnesium (Mg) (mg)	216.6 ± 45.64	166.27 ± 24.94	0.361
Besi (Fe) (mg)	5.89 ± 1.13	4.48 ± 0.67	0.312
Zinc (Zn) (mg)	5.36 ± 0.83	4.4 ± 0.31	0.315

Data are presented as mean ± standard deviation. p values: Mann-Whitney test

increase insulin resistance. Dietary habits or diet, especially carbohydrate and lipid types, are important determinants of insulin resistance. Several previous studies have shown that carbohydrate and fat intake was associated with the incidence of T2DM. High-calorie and high-fat diet will increase insulin resistance even in low-risk populations [14, 24, 25]. The high lipid intake in the GSTM1 null compared to GSTM1 positive was found to have a significant relationship between this gene variant. We suggest further research whether these two risk factors are interr-elated risk factors of T2DM.

The mean of vitamins C and E intake were lower in GSTM1 null than GSTM1 positive. Lower intake of vitamins C and E in the null group compared to the positive group was also found in the GSTT1 gene. Significant differences were found in the mean of vitamin E intake in GSTM1 and GSTT1 positive compared to GSTM1 and GSTT1 null ($p < 0.05$), but not in vitamin C. Vitamin C and vitamin E are claimed to be antioxidants that reduce oxidative stress and ROS. As an antioxidant, vitamin C is known to reduce insulin resistance by improving endothelial function thereby preventing the development of T2DM. Insulin resistance and lack of insulin production are caused by oxidative damage to β cells due to excessive ROS in the body and triggering fat peroxidation. Vitamin C works by donating its electrons to fat radicals to end the chain reaction in the fat peroxidation process. Vitamin E is the

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main antioxidant in cell membranes. Previous studies have shown a protective effect of vitamin E intake against the incidence of type 2 diabetes. The action of vitamin E influencing glucose tolerance, insulin sensitivity, and insulin secretion is not yet understandable [26, 27].

In addition to macronutrient and vitamin intake, this study also assessed differences in the mean mineral intake of calcium, magnesium, iron, and zinc in the GSTM1 and GSTT1 variants. Insulin secretion is a calcium dependent process while calcium is one of the activator components of Calcium receptors (CaR). CaR can mediate cell-to-cell communication, including cells in the pancreas that allow changes in extracellular calcium (Ca2+) concentrations. Cell communication is mediated by CaR and allows β cell response to secrete insulin. Magnesium (Mg) is a mineral that makes it easy for glucose to enter cells and cofactor of various enzymes for glucose oxidation. Previous study showed low magnesium intake leading to impaired insulin secretion whereas magnesium supplementation decreased the incidence of T2DM [28, 29, 30].

Zinc (Zn) is known to improve the structure, synthesis, storage, and secretion of insulin so that they can synthesize glucose transporters that were translocated from intracellular to the plasma membrane. Glucose transporters help glucose molecules cross the cell membrane and reduce glucose buildup outside the cell. As a hemoglobin forming material, iron (Fe) is also considered important in the pathogenesis of T2DM. Macronutrient metabolic processes (carbohydrates, fats and proteins) require oxygen as a basic compound. Transport of oxygen is carried out by hemoglobin. Lack of Fe in the body causes lower amount of hemoglobin and reduced amount of oxygen being transported. Disruption of the oxygen transport process causes impairment of carbohydrate metabolism so that blood glucose levels are uncontrolled which causes an insulin resistance [31, 32].

Interestingly, this study found the mean levels of calcium, magnesium, zinc, and iron in the GSTM1 and GSTT1 null were lower than those in GSTM1 and GSTT1 positive. Some previous studies showed that GSTM1 and GSTT1 null act as a risk factor of T2DM. Further research needs to be done by including healthy subjects to analyze dietary intake and its role in GSTM1, GSTT1 gene variants as risk factors of T2DM.

Conclusions

This study concluded that there were significant differences in mean lipid intake, RDA lipid %, lipid % carbohydrate, and vitamin E intake in GSTM1 positive compared to GSTM1 null. There were also significant differences in the mean of energy, vitamin E, and calcium intake in GSTT1 positive compared to GSTT1 null in T2DM patients at USU Hospital, Medan, Indonesia.

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Conflict of Interest

The authors declare no conflict of interest.

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Original Research

Comparison of nerve conduction parameters in type 2 diabetic subjects: recently diagnosed versus chronic diabetes

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Abstract

Introduction: Diabetes mellitus (DM) is one of the major non-communicable diseases and may cause blindness, renal failure, and non-traumatic limb amputations in chronic condition. Periodic clinical assessment with supportive electrophysiological tests is highly recommended for early diagnosis of peripheral neuropathy in diabetic patients. **Materials and Methods:** In order to compare the nerve conduction study parameters on diabetes with two different durations of the disease, the recruited diabetic patients were divided into two groups, Group I - Recently diagnosed type 2 diabetes (within 1–2 years) and Group II -chronic diabetic patients with more than 5 years of disease. Nerve conduction study was done with RMS-EMG machine and latency, duration, and amplitude parameters of sural nerve conduction recordings were measured. The significance of study parameters between groups was analyzed by using independent sample "t" test. **Results:** There is no statistically significant change in the latency, amplitude, and conduction velocity of the sural nerve among the aforesaid study groups.

Keywords: Diabetic neuropathy, nerve conduction study, sural Nerve.

Introduction

Type 2 diabetes is a major public health issue and the expected worldwide diabetes population could surpass 640 million by the year 2040 [1]. India and China together have become a global epicentre of the diabetic epidemic as 60% of the world's diabetic population is from Asia [2]. Microvascular complications such as nephropathy, neuropathy, and retinopathy and macrovascular complications such as stroke, and peripheral artery disease are common among chronic diabetics and accountable for significant morbidity and mortality [1].

Diabetic neuropathy involves damage in sensory, motor, and autonomic nerve fibres and accounts for 28% complications in diabetics [3]. It is the crucial risk factor in 90% of diabetic foot ulcers [4] and foot ulceration is the first indicator in diabetic patients, who underwent non-traumatic lower-limb amputations later [5]. As the appearance of symptoms of diabetic neuropathy occurs after a long duration of disease, it is imperative to identify diabetic neuropathy in the early stage itself. Clinically, the monofilament test, vibration test, tests for pinprick sensation, and ankle reflex are generally employed in the diagnosis of diabetic neuropathy [4]; however, electrophysiological studies help us to detect early abnormalities in diabetic patients that may not be clinically apparent [6].

Nerve conduction study is a widely used electrodiagnostic test to assess the nerve functions in diabetic neuropathy, which affects the nerve conduction velocity, amplitude, and latency. As the complications of neuropathy show its symptoms after many years of diabetic duration, we wanted to know whether the neurophysiological

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test shows any changes in the earlier years. This study was done to compare the nerve conduction parameters in the diabetics of recently diagnosed (1–2 years) and chronic (> 5 years).

Material and Methods

This cross-sectional study was conducted after obtaining approval from the Institutional Ethical Committee and written informed consent from the participants concerned. This study was undertaken in the Department of Physiology in collaboration with Department of Medicine, Sri Manakula Vinayagar Medical College and Hospital, Puducherry, India.

Study subjects

The diabetic patients who attended the Medicine OPD in the institutional hospital were recruited and study subjects were divided into two groups as following.

Group 1: Recently diagnosed T2MD patients (1–2 years prior to the study) (n = 24)
Group 2: Chronic type 2 diabetes mellitus (T2DM) patients (>5 years prior to the study) (n = 24)

Sample size

Based on the study, conducted by Nidhi Yadav et al [7], the mean values of sural nerve conduction velocity in T2DM (45.58±3 m/s) and control subjects (49.05±4 m/s) were taken into account and the requisite sample size for this study was calculated by considering non-response rate as 10% by using OpenEpi software (version 3.01). The estimated requisite total sample size is 48 (n) and 24 samples for each group.

Inclusion and exclusion criteria

T2DM patients in the age group of 40–70 years including both genders, who were recently diagnosed (within 1–2 years prior to study) and chronic (>5 years prior to study) were recruited for the study.

Type 2 diabetic patients with any medical condition associated with polyneuropathy, unusual dietary habits, family history of peripheral nerve disease, consumption of alcohol or drugs with potential neurotoxic effects, and dependent on insulin therapy were excluded in the study. Also, type 1 diabetic patients were omitted.

Study parameters

A detailed review of medical history through a structured questionnaire and physical examination were performed. In addition to the patient's age, the anthropometric data including height, weight, and body mass index (BMI) were acquired from the study participants. Body mass index was calculated by using the formula, i.e. body weight in kg/(Height in meters)^2.

Nerve conduction study was systematically performed with all the study participants (Group I, n=24 and Group II, n=24) by using surface electrodes of computerized RMS EMG System. In the present study, three parameters of nerve conduction study namely nerve conduction velocity, amplitude, and the latency of sural nerve were measured.

Statistical analysis

The values are expressed as mean ± SD and the statistical significance of the test parameters between the study groups was compared by using an independent sample 't' test, executed with the EpiData Analysis software package (version 4.5). A "p" value of <0.05 was considered to be statistically significant.

Results

The mean value with standard deviation in the participant's age, duration of diabetic diagnosis prior to the study, and anthropometric data of height, weight, and BMI of the study subjects are given in the under mentioned table (table 1).

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The mean values of latency (ms), amplitude (μV) and velocity (m/s) of sural nerve in Group I (recently diagnosed diabetic patients) were 2.78 ± 0.49, 13.22 ± 5.38 and 52.53 ±6.78, while in Group 2 (chronic diabetic patients) were 2.88 ± 0.466, 12.64 ± 5.70 and 49.67 ± 7.59 (table 2). Though there is an increase of latency and decrease in amplitude and conduction velocity in diabetic patients of long duration (>5 years) compared to diabetic patients recently diagnosed (<2 years), the difference is not statistically significant (figure 1).

Table 1: Patient's age, duration of diabetes, and their anthropometric data (Mean ± SD).

	Group I (n - 24)	Group II (n - 24)
Patient's age (years)	48.04 ± 5.27	62.1 ± 7.66
Duration of diabetes (years)	1.12 ± 0.46	7.16 ± 2.09
Height (cm)	154.62 ± 12.97	152 ± 11.74
Body weight (kg)	59.08 ± 11.12	57.8 ± 9.95
Body mass index	25.51 ± 7.88	25.45 ± 6.34

Table 2: Nerve conduction study parameters in sural nerve (Mean ± SD).

Study Parameters	Group I (n - 24)	Group II (n - 24)
Latency (ms)	2.78 ± 0.49	2.88 ± 0.466
Amplitude (μV)	13.22 ± 5.38	12.64 ± 5.70
Velocity (m/s)	52.53 ± 6.78	49.67 ± 7.59

Discussion

This present study showed that there is no statistically significant difference in the nerve conduction parameters viz. latency, amplitude, and velocity of sural nerve between the study groups. The consideration of sural nerve in this study is due to the fact that this nerve is the first affected and also a most prevalent indicator of peripheral nerve dysfunction [8]. Although polyneuropathy is uncommon in the initial stage of diabetes, existence of polyneuropathy during the diagnosis of T2DM is seen in many cases due to late diagnosis of the disease [11]. The experimental design of this study entailed to compare the results of the nerve conduction test of sural nerve of the chronic diabetic patients from recently diagnosed diabetic patients and study results showed that there is no significance change in any of the three test parameters (latency, amplitude,

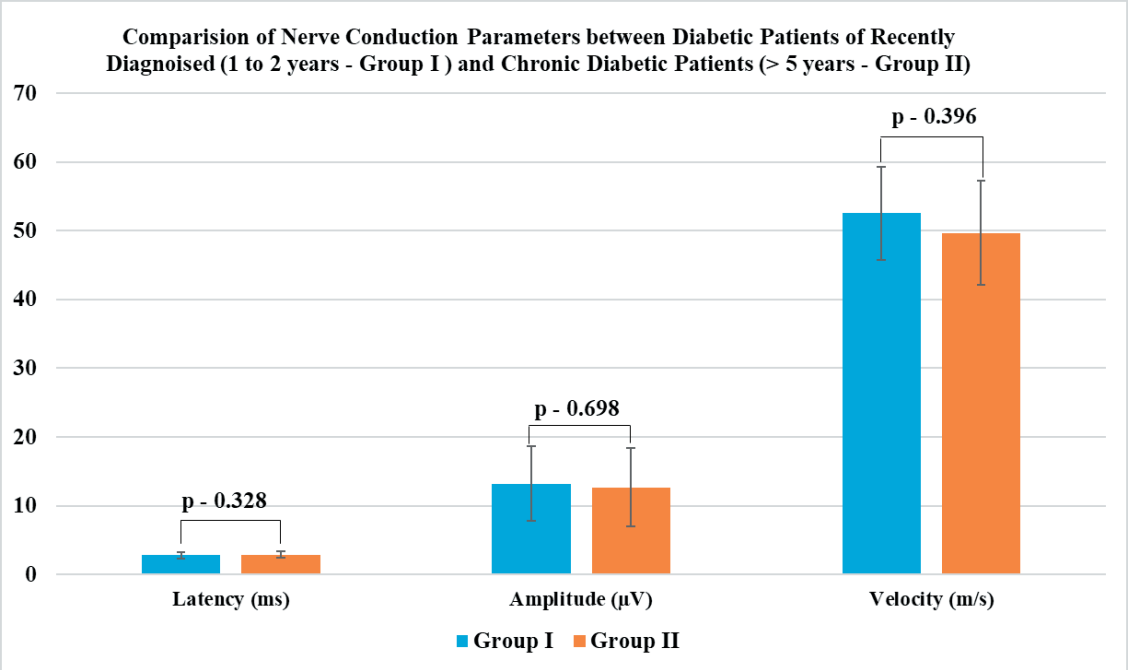

Figure 1: Graphical representation of mean values with standard deviation of nerve conduction parameters (p values are given).

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and velocity). On the contrary, the published study of Gauhar Hussain et al on 2014 demonstrated significant reduction of a nerve conduction velocity in lower limbs even in patients of shorter duration while they have normal nerve conduction velocity in upper limb [12].

Sonawane P. P and Shah S. H (2017) performed the nerve conduction test in the groups of diabetic patients, i.e., 0–5 years diabetic patients and 5–10 years diabetic patients, both having controlled blood sugar levels and it was revealed that sensorimotor conduction is reduced in the lower limb over the duration of diabetes [13].

Apart from the duration of the disease and degree of hyperglycemia, diabetic neuropathy is also associated with other risk factors such as dyslipidaemia and hypertension [9] and it has been revealed that chronic diabetic subjects with a duration of more than 10 years have associated neuropathy and therefore, they are at high risk for diabetic foot disease [10]. The levels of glycosylated Hb (HbA1c) and lipid profile were not correlated with the parameters of the nerve conduction test and it is the main limitation of this study. If selection of patients and comparison of groups based on their HbA1c values were done, the study would have given more meaningful results.

Conclusion

The present study results show that there is no correlation between duration of the disease and the occurrence of peripheral neuropathy. Few other recent studies also establish the same results. Therefore, further studies with more sample size and with all relevant parameters are warranted to rule out the specific causes of diabetic neuropathy.

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Conflict of Interest

The authors declare no conflict of interest.

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Review

Patterns used in weight loss in patients with obesity: A literature review

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Abstract

Background and Aims: Obesity is one of the most common co-morbidities in the world and is on the rise. This article aims to analyze the nutritional approaches of these patients, analyzing as many food patterns as possible. **Material and Method:** We analyzed the literature available in the fields of PubMed and Scopus using the following filters: obesity management, dietary patterns in obesity management, diets for weight loss, and lifestyle intervention among obese patients. We have selected articles published exclusively in English, between 2014 and 2020. **Results:** A multitude of dietary patterns are published in order to help obese patients lose weight, but the difficulty of this process and cardiovascular risk can be influenced by severe diets, intense hyper lipidic. **Conclusions**: The implementation of a healthy diet, through food re-education, could lead to a weight loss similar to different food patterns, not only without increasing mortality but with increasing the health status of the patient.

Keywords: Diet, healthy eating, low-carb, obesity, weight management.

Background and Aims

Obesity is one of the most terrifying pathologies affecting, according to the World Health Organization, by 2016, over 650 million adults, over 340 million adolescents, and most worryingly, over 38 million children under the age of 5. It is important to note that these values represent a tripling of the 1975 incident [1].

Material and Method

The selection of the studies was made in the PubMed and Scopus platforms. The search terms from which the studies were selected are obesity management, dietary patterns in obesity, diets for weight loss, and lifestyle intervention among obese patients. Studies published in the period 2014–2020 were analyzed and those published in English were chosen exclusively.

Results

One of the key factors about obesity, also highlighted by the World Health Organization (WHO), is that this growing disease is completely preventable. The way we can do this is the purpose of this review, by analyzing the most current guidelines for managing obesity, maintaining health with an optimal nutritional

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intake and, last but not least, by analyzing the various food patterns addressed today, not always with the physician approval [1].

The definition of obesity consists in a body mass index (BMI) greater than or equal to 30 kg/sqm, according to the calculation formula: BMI = G/T $(m)^2$ [1].

The causes that favor the development of obesity in both adults and children consist in the increased intake of foods with high caloric density, with a higher weight for the intake of lipids and sugars, at the same time with the decrease in physical activity [1]. Each of these two factors has an extraordinarily strong effect, but when they are found together in the same individual the effects are potentiated and the risk of weight gain is much higher.

In 2020, the WHO claims that obesity, in order to be combated, must be acted upon in two directions: at the individual level, it recommends that the intake of lipids and sugars decrease, increase the intake of fruits, vegetables, cereals, oilseeds and increase the level of physical activity, and at the industrial level supports the reduction of the use of fats, sugar and salt from processed foods as well as ensuring that consumers have as many healthy food options at hand [1].

Thus, obesity becomes a serious, worrying condition that can be prevented through good collaboration in society and the individual.

Recommendation of the Guidelines

To meet the practitioners who work with overweight patients come several guidelines that present their approach from a nutritional point of view.

The European Guide to Focusing on Obesity Management proposes that the right attitude in guiding an obese patient should start with improving communication with him, which is essential for adherence to nutritional therapy and motivation. Also, it is very important to avoid stigmatizing the patient as well as to clearly set weight loss goals, from the first visit (between 5 and 10% of the current weight) [5].

Obesity is an extremely complex pathology that affects the patient both physically, where a careful evaluation of the patient is recommended (current weight, maximum weight, abdominal circumference, evaluation of co-morbidities), and mentally, which is why the motivational interview is recommended to assess whether the patient is at the right time to start a weight loss program [5].

The initial recommendations of the European Guide do not contain strict measurements regarding food consumption, but rather recommend starting the program with lifestyle improvement, for a food discipline, avoiding weight fluctuations and increasing the level of physical activity. These interventions can lead to an achievement of the initial weight loss target in the proportion of 15–65% of the initial target [5].

General lifestyle optimization recommendations for obese patients include:

- Decreasing the caloric density food consumed by increasing the intake of vegetables, decreasing the intake of saturated lipids, refined carbohydrates, sugar, and sweetened drinks; decreasing the size of portions and consuming at least two fruits/day [5].
- Arranging the plate with half of it from vegetables [2]
- Increasing the palatability of food by adding spices and herbs [2]
- Keeping a food schedule as clear as possible, avoiding snacks or skipping meals [5].
- Discipline the body, by keeping the food schedule, to consume food when hunger occurs (hunger is defined as a sensation that occurs 4–5 hours after the last meal, felt as a "hole in the stomach" accompanied by a "specific noise") and stop eating when the state of satiety appears [5].
- Keeping a food diary [5]
- Adding low calorie density foods to appetizers (soup, appetizer salad, fresh fruit) [2]

Current Food Patterns

In addition to all these healthy eating recommendations for weight loss by adopting optimal, balanced nutrition, more and more studies of food patterns have been described in

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the literature aimed at the exchange between the percentages of macronutrients, but keeping the same total energy consumption.

One of the most often used type of diet that aims to lose weight as fast as possible is the variant in which the carbohydrate intake decreases, as a total percentage in energy consumption.

Many publications blame carbohydrate intake, promoting it as unhealthy food. This theory is based on the idea that our ancestors, 50,000 years ago, consumed almost no cereals or starchy vegetables, the diet known as Paleo, and were limited to a maximum carbohydrate intake of about 35% [9].

Kaplan et al. [10] studied the population of Tsimana in South America, an extremely poor area that was found to have a macronutrient distribution of 72% carbohydrates, 14% protein, and 14% lipids. Despite this high carbohydrate intake, without general recommendations, this population has the lowest reported level of chronic diseases worldwide. The conclusion of this analysis was that the quality and not the quantity of carbohydrates is the key to a healthy diet [10].

In addition, Mazidi M et al. [15] published a study involving 24,825 subjects who analyzed all causes of mortality as well as specific causes of mortality for patients on a low-carb (LC) diet. The published results consisted of an overall increase in mortality of 32%, increased frequency of mortality due to cardiovascular causes (50%), cerebrovascular causes (51%), and cancer (36%). The authors conclude by saying that there is a significant association between LC diet and mortality of any cause and specific cause [15].

A hypoglycemic diet involves a carbohydrate intake below the minimum accepted limit, below 130 g/day. Another option is an intensely hypoglycemic diet in which the carbohydrate intake decreases between 20 g and a maximum of 50 g/day [4].

By decreasing carbohydrates intake, there are two other macronutrients that can be increased, proteins, or lipids.

Hyper protein diets have an increased amount of protein which leads to a very large and very rapid increase in satiety by increasing the concentration of cholecystokinin, GLP-1 and PP Y, as well as increasing the amount of amino acids and gluconeogenesis [6].

If the carbohydrate intake is low, then the amount of insulin is also decreased, decreasing lipogenesis and increasing lipolysis, which together lead to a very rapid weight loss. But if the intake of carbohydrates continues to be well below the minimum amount needed by the body, the central nervous system will use alternative ways of producing energy, a phenomenon that will lead to the appearance of ketone bodies.

Kim Bo-Yeon [6] studied the effects of the low-carb, high-fat diet (LCHF) on body weight, cardiovascular risk, and mortality. From the cardiovascular system point of view, in a prospective cohort study, LCHF diets with predominant fat intake from animal sources, led to an increased association with an increase in mortality from any cause and from cardiovascular cause in patients who have previously suffered a myocardial infarction [7].

The same diet, but from plant sources, called "Eco-Atkins" by Jenkins DJ et al [8] led to an improvement in LDL cholesterol compared to a hyperglycemic diet [8].

Therefore, as well as in the low carb pattern diets, so it happens in high lipid diets. It is not about the amount, but about the quality of food.

Sajjadi SF et al. [11] aimed to analyze if a low-carb diet can produce any modification to the metabolic rate. They did that by analyzing a group of 304 obese women by BMI, body analyses (percent of fat, percentage of lean mass, visceral fat), and basal metabolic rate measured by indirect calorimetry. Patients were divided into three groups in terms of the value of basal metabolism compared to the standard: below the standard, within its limit, and above. The composition of the diet of enrolled subjects was analyzed using a standardized, semi-quantitative, food frequency questionnaire.

The conclusion was that the LC diets did not show any statistical significance between the groups but the components of the diet such as sugars, refined cereals and monounsaturated fatty acids (MUFA) showed statistical significance between the three groups [11].

Another nutritional approach to weight loss is intermittent fasting. This involves either the classic option, in which the patient has at

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least one day of fasting or the time-restricted diet, in which the patient follows complete digestive rest at a certain time of day, every day [4].

A 12-week trial that included 32 obese subjects who followed the pattern of intermittent fasting, meaning that on fasting days they had an energy intake of 25% of the total, and the rest of the days they ate without restrictions, they presented a weight loss of 5.2 kg compared to the control group on which no nutritional intervention was applied [12]. In another trial that aimed to compare weight loss over a period of 1 year, between 3 groups, one of intermittent fasting (25% of NC), one of calorie restriction (75% of NC) and another without intervention, showed no difference between the groups that had a nutritional intervention [13].

Another relatively new approach to dieting for weight loss is the "Calorie Shifting Diet," in which patients receive a different caloric intake, either overnight or differently between groups of days.

Such a diet was studied by Davoodi SH and his collaborators [14], in the trial in which he enrolled 74 sedentary, obese patients. The study was conducted over a period of 10 weeks, six with active nutritional intervention and four follow-ups. Patients were divided into two groups in terms of nutritional intervention: the first group was CSD, in which patients had 11 days with four meals/day, at an interval of four hours, followed by three days without restrictions, and the second group, CRD, followed a balanced and constant diet in terms of macronutrients throughout the study. The minimum energy contribution in both ruptures was 1100 kcal. At the end of this trial, it was found that weight loss, satiety, and eating comfort were similar between the two groups but the average RMB decreased less in the CSD group [14].

Conclusions

The more attention is paid to the real problems caused by obesity, the more the variants in nutritional intervention and trials that confirm or refute certain ideas of food patterns appear.

Table 1: Different dietary patterns and the basic recommendations. Adapted from 2, 3, 4.

	Kcal/day	Proteins (%)	Carbohydrate (%)	Lipids (%)	Fiber (g)	Recommendations
Low calorie balance diet	1000–1500	10–35	45–65	20–35	20–35	Low-calorie variants of healthy diets: • Mediterranean diet: high levels of monounsaturated lipids and low levels of saturated lipids; increased consumption of fruits, vegetables, grains, and starchy vegetables • DASH diet: 4/5 servings of fruits and vegetables/day; low fat dairy products
Low fat diet	1000–1500	10–35	45–65	<30	20–35	• Increased intake of fruits, vegetables, whole grains, starchy vegetables • Consumption of proteins with lipid intake as low as possible • Saturated lipids <10%
Intense low-fat diet	1000–1500	13–20	70–77	10		
Low carb diet			26–45	20–35		50–130 g carbs/day
Intense low carb diet			<26	20–35		20–50 g carbs/day

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Restrictive variants help more or less but what is really clear is that a nutritional intervention that involves a dietary re-education of patients shows weight loss and increase in patients' quality of life similar to restrictive, low-calorie variants with or without certain clear dietary patterns.

The studies included in this article have highlighted that the quality and not the amount of carbohydrates can be the key to losing weight and/or maintaining optimal health when approaching the style with a diet high in carbohydrates.

On the other hand, the LCHF diet can be extremely harmful or can be healthy, with the same amount of lipids, but it is extremely important if these lipids are of vegetable or animal origin, mortality being higher in patients with high animal lipid intake compared to those with an increased intake of vegetable lipids.

Conflict of Interest

The authors declare no conflict of interest.

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Review

Obesity, a disease of the modern society

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Abstract

Background: Nowadays, the aging of society, the lifestyle changes at the population level, the modern dietary pattern, and the low level of physical activity have an adverse effect on the waist line and the Body Mass Index (BMI). **Methods:** Based on scientific literature, we have drafted a review on excess weight and obesity around the world. The mean BMI is an important determinant of health at the population level. We used the WHO database for the years 1975–2016 as starting point and we predicted the average BMI around the world until the year 2100 using Microsoft Excel trendline equation. **Results:** Our findings are the first that estimate excess weight and obesity trends globally until 2100. This study adds growing evidence that the weight status will significantly affect all continents. We identified regions known with a low rate of obesity : East Mediterranean, South-East Asia, Western Pacific, and Africa will encounter severe weight issues. Generally, our data shows that the underdeveloped countries are less likely to report significantly higher rates of obesity by 2100, compared to the developed countries. **Conclusions:** There is growing evidence that weight gain at the population level is associated with a modern lifestyle and the psychosocial environment.

Keywords: adipose tissue, energy expenditure, BMI, obesity, pandemics, lifestyle.

Problem Statement

Obesity is currently considered a complex, recurrent, chronic multifactorial disease, arising as a consequence of genetic factors, obesogenic environment [1], and neuroendocrine mediation [2]. Obesity is linked to socioeconomic factors such as the behavioral model, lifelong experiences and the perceived environment. The modern lifestyle, including sedentary use of time, over-eating behavior, hedonic output, and the environmental factors disrupt the metabolic efficiency and predispose the individuals to weight gain. Excessive body weight is one of the major leading causes of preventable and premature death worldwide and increases the risk of morbidity and mortality [3], leading to cardiometabolic diseases, chronic respiratory diseases, and cancer. For the first time in human history, life expectancy is declining for the present generation compared to the previous one [3].

By 2050, more than 462 million new cases of cardiovascular disease and 212 million new cases of diabetes will occur due to overweight and obesity [4]. Although over time, obesity has been linked to genetic and biochemical mechanisms, the non-genetic risk factors strongly modulate the individual risk of weight gain. The main determinant of the obesity pandemic is chronic overeating and the high-calorie intake. Obesity is closely related to the economic status of the population. Globalization, together with sedentary behaviour, and the low energy expenditure are important drivers of the obesity pandemic. Data currently

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available show that there are regional differences in both excess weight and obesity trends [5]. In developing countries the arising prevalence of obesity occurs due to chronic stress, common inappropriate habits such as physical inactivity, unhealthy diet, and hypercaloric food consumption [6]. A lower Socioeconomic Status (SES) is related to restricted healthy lifestyle opportunities that could lead to more stress and consequently increase in stress hormones, which increase fat deposition and visceral fat [7]. Lifestyle changes should start with effective control of the most common risk factors: smoking, sugar intake, alcohol consumption, sedentary behaviour [8].

Background

The hypotheses of the adipose tissue expansion have evolved over time. The genetic factors alone are not responsible for the rising prevalence of obesity, but rather, the negative lifestyle changes of the entire population and the obesogenic environment are the starting point [9]. The mismatch between energy expenditure and energy intake leads to lipid storage in the human body. Abnormal or excessive fat accumulation may impair health. The modern lifestyle leads to low level of energy expenditure due to unhealthy eating behavior associated with screen-based sedentary time, low cardio fitness levels and lack of sleep [10]. The nutrition transition- modernization, urbanization, and economic development- increased, worldwide, the shifts in diet, which means that local seasonal food has been replaced with tasteful, non-perishable, easy to procure, transport, store and east to prepare high-density meals [11, 12]. It is well known that the cheapest calories come from food oils and carbohydrates, and on the other hand, healthy food, rich in vitamins, macronutrients and micronutrients is more expensive. The main energy storage of the body is fat, which can be stored in large amounts, unlike proteins and carbohydrates [13]. Overeating and weight gain at the population level is achieved through increased content of kilocalories, lipids, carbohydrates, and a low dietary fiber content [14]. Sedentary behavior as total sitting time, screen time in absence of physical activity are an independent risk factor for weight gain, chronic diseases, and premature mortality [15]. The daily energy expenditure includes the basal metabolic rate, the energy expended through thermogenesis during physical activity and non-exercise activity thermogenesis (NEAT) [16]. NEAT is the caloric energy expended through activity outside of structured exercise. The molecular basis involved in the non-physical activity thermogenesis (NEAT) remains unknown and is closely related to excess weight. It is well known that a high proportion of individuals spend more than 70% of their daily energy expenditure as a result of the resting energy expenditure (basal metabolism) and a very low proportion of the caloric consumption as a result of the baseline fitness activity [17]. This hypothesis shows that a leading cause for excess weight nowadays may be linked to all bad habits of the modern lifestyle that lower the body's metabolism [18]. Eating patterns are involved in the aetiology of several chronic diseases including obesity. Visual and olfactory food stimuli contribute to weight gain. The level of physical activity can be adversely affected by weight gain. Countless studies have correlated an increased level of physical activity with a better health status, proving that aerobic activity reduces all causes of mortality [19]. Frequently, the built environment and its characteristics, such as walkability of the urban sprawl, the residential density, the street connectivity, and the land use mix correlate with a low cardio fitness level in the general population. The sedentary lifestyle was found to be positively associated with a downregulation of the metabolic rate and weight gain. Also, the lack of physical activity plays a big part in overall prognosis. Compared to rural areas, the urban environment, through its specific architectural design, discourages physical activity, such as walking or cycling, as more and more individuals spend their leisure time in screen-based sedentary activities [3]. Therefore this association modifies the eating habits and increases snack consumption in front of the screens. In modern society, circadian rhythm disturbances are more frequent and occur due to night shifts, irregular sleep schedule, exposure to artificial light at night and time zone

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changes when flying to another time zone [20]. Short-term sleep deprivation causes weight gain through lipid metabolism disorders [20] and leads to long-term effects on cellular responses, called "metabolic memory" [21]. Clinicians commonly use in the medical practice the index of weight for height, known as Body Mass Index (BMI) in order to classify overweight and obesity in adults. A BMI greater than or equal to 25 is considered as overweight. A BMI greater than or equal to 30 indicates obesity [22]. As for the Asian and Indian populations, according to the latest classifications the cut-off point for the ideal weight BMI score is between 18.5 kg/m^2 and 22.9 kg/m^2 [23, 24]. A BMI between 26kg/m^2 and 31 kg/m^2 may predict a high risk [25]. High-calorie intake, sedentary lifestyle, and low level of energy expenditure have a detrimental effect on the BMI. The mean BMI is increasing across the world with an impressing rate along with globalization and urbanization level. Acording to CDC data, obesity has reached pandemic proportions [22]. Unfortunately, obesity is interconnected to noncommunicable diseases, such as cardiometabolic, respiratory, and oncological diseases, meaning that the impact of adiposity may be estimated by the NCDs mortality. Each year, noncommunicable diseases kill 80% of people worldwide [3]. It is well known that obesity is closely related to the economic status of the population. Anthropometric measures should take into account contextual environment in which individuals live [26].

Aims and Research Method

Obesity is an expanding global health issue. Excessive intake of energy-dense food together with a low level of physical activity, has led to a pandemic of obesity and noncommunicable diseases [22]. This study provides data of excess weight and obesity in adults for the next decades using the latest WHO reported data. Our aim is to estimate worldwide trends in mean BMI and to predict obesity rates in adults from the year 2030 to the year 2100. The method of research analyzes the available data for the mean BMI between 1975 and 2016. Using Microsoft Excel trendline equation, we estimated the mean BMI rates across the world until 2100.

Findings

Our analysis shows that by maintaining the actual trends in growth of obesity all around the world, by 2100, even the regions with low

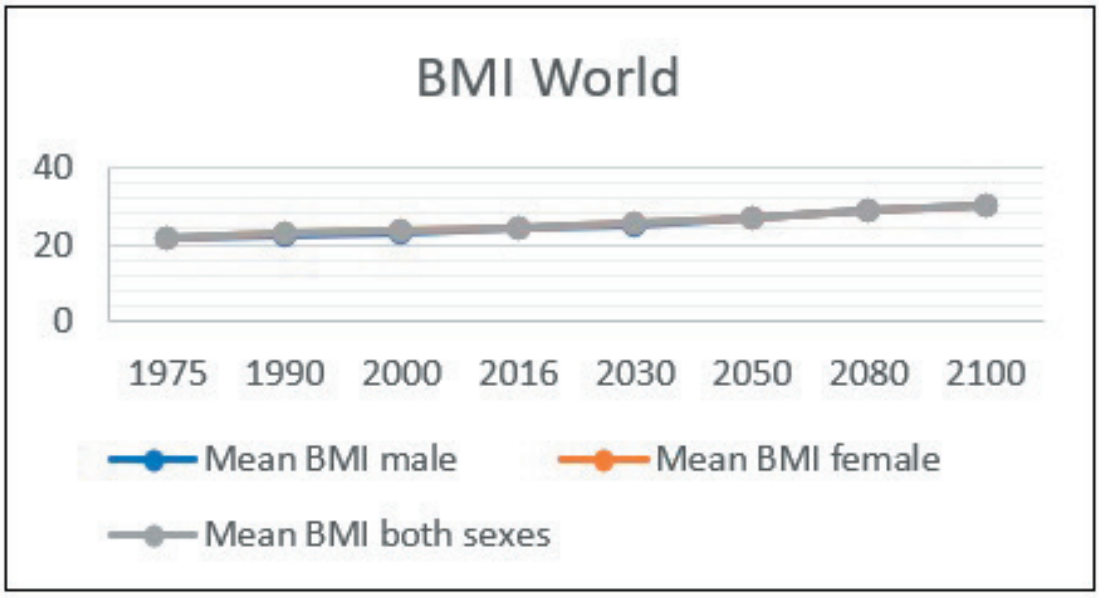

Figure 1: Mean BMI World (own calculations using WHO data). Source: WHO data [3].

rates of excess weight and obesity will be affected similarly to the ones with higher rates.

We predicted that weight gain will increase in all regions of the world, also affecting the areas with a low rate of obesity such as: East Mediterranean, South-East Asia, Western Pacific, and Africa. We also identified that the income of the population has a large impact on the ability of both men and women in maintaining a healthy weight. If the actual trends of weight gain maintain the same pattern at the population level, the mean BMI will increase worldwide. Generally, our data show that the upward trend of weight gain, a mean BMI score about 30 kg/m^2 globally for both sexes, both in low-income and high-income countries will be reached by 2100.

According to WHO data, the mean BMI remained relatively stable worldwide until 2016 with a maximum value of 24.5 kg/m^2 for both sexes. Our data shows gradually increasing rates between 2030 and 2100. Our estimated mean value of the BMI for 2030 is 25.4 kg/m^2, while for 2050 the mean BMI increases at a value of 26.8 kg/m^2. As for the year 2080 our estimated value is 28.9 kg/m^2, showing that the European population may be affected by excess weight. We estimated that in 2100, the male population will be affected by obesity with a mean BMI value of 30 kg/m^2 for men and 29.85 kg/m^2 for women. The mean value for both sexes will reach 30.27 kg/m^2. Thus, the cutoff values for BMIamong populations such as the Asian or the Indian populations are different [23, 24]. For a better approach on the trend of excess weight and obesity, we analyzed separately the average BMI value in different regions of the world.

The strongest associations with weight gain are found for the social capital [27]. Nowadays, high income countries have a higher prevalence of obesity. The WHO data show that in the low income population, before 2016 the average BMI score was below 25 kg/m^2 for both sexes. The low income category of population is more likely to be overweight by 2100. According to our analysis, the female population is more susceptible to be overweight. Until 2016, the mean BMI value was 22.4 kg/m^2 for both sexes in the low income countries. In 2030 our estimated mean BMI value for females reaches 24 kg/m^2. Our data shows that the mean value of the BMI exceeds the normal cutoff values with a 25.6 kg/m^2 value beginning with 2050, in 2080 it reaches 28.1 kg/m^2, while in 2100 it increases towards obesity cutoffs, with a mean value of 29.7 kg/m^2. As for the male population living in low income countries, our data reveals that the men living in these countries might be overweight in the next decades. Their BMI values will increase from 22.6 kg/m^2 in 2030 at 23.6 kg/m^2 in 2050, 25.1 kg/m^2 in 2080 and 26.1 kg/m^2 in 2100.

In the high income population, the average BMI score across the world had high values in 2016 with a value of 26.5 kg/m^2 for both sexes. Using the trendline equation, we identified that the male population will be more affected by obesity until 2100. In 2030 the mean BMI value will be 28 kg/m^2, 29 kg/m^2 in 2050, 31.5 kg/m^2 in 2080 and 32.8 kg/m^2 in 2100. As for the female population living in high income countries, our prediction shows that in 2030 their mean BMI score will reach 26.9 kg/m^2, 28.1 kg/m^2 in 2050, 29.7 kg/m^2 in 2080 and 30.4 kg/m^2 in 2100.

Until 2016, in the European region, the maximum average BMI score for both sexes was 26.4 kg/m^2. Our prediction shows higher rates of average BMI for the male population with a value of 27.6 kg/m^2 in 2030, 29 kg/m^2 in 2050, 31.1 kg/m^2 in 2080 and 32.4 kg/m^2 in 2100. In the European female population, these rates may also increase between 2030 and 2100. Our analysis shows an average value of the BMI of 26.5 kg/m^2 for 2030, 27.1 kg/m^2 for 2050, 28.1 kg/m^2 for 2080 and 29.7 kg/m^2 for 2100.

Regions such as East Mediterranean and South-East Asia, known for a healthy lifestyle are also affected by excess weight and obesity. In 2016 in the East Mediterranean region, the average BMI for both sexes was 26.1 kg/m^2. For women this score was higher, reaching the value of 27 kg/m^2 and 25.3 kg/m^2 for the male population. Data shown in our prediction reveal an ascending trend of obesity until 2100, when the average BMI in the East Mediterranean region will reach 33.4 kg/m^2 for both sexes. In 2030 the mean BMI score in the East Mediterranean population will

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be 27.3 kg/m^2. In 2050, the mean BMI will reach 29 kg/m^2 and 31.7 kg/m^2 in 2080 for both sexes. According to our estimations, the average BMI in 2100 will be higher in women than in men, reaching the average BMI value of 35.4 kg/m^2 for women and 32.6 kg/m^2 for men.

Regarding the South-Eastern region of Asia, the average BMI value for both sexes in 2016 was 24.5 kg/m^2. The female population had a mean BMI score of 24.6 kg/m^2 and the male population a BMI score of 24.3 kg/m^2. According to these values the Asian population is already overweight.

We estimated that in the further period of time in the Asian population the average BMI score will be 25.4 kg/m^2 for 2030, 26.8 kg/m^2 for 2050 and 28.8 kg/m^2 for 2080. If the weight gain continues with the present rates, by 2100 the Asian population will be severly affected by obesity with an average BMI value for both sexes of 30.2 kg/m^2. This index will be slightly higher in the Asian male population with an average BMI value of 30 kg/m^2 and lower in female population with an average BMI score of 29.85 kg/m^2.

In the United States of America, in 2016, the obesity rates were very high with a maximum average BMI score of 29 kg/m^2 for both sexes. By 2100 the values of the average BMI will be among 35 kg/m^2, higher in women than in men. The male population living in the USA will reach increasing BMI values, starting from 28.5 kg/m^2 in 2030, increasing gradually. We determined a 30.16 kg/m^2 value for 2050, 32.6 kg/m^2 for 2080 and 34.2 kg/m^2 for the year 2100. As for the female population living in the Americas, our prediction shows that in 2030 their average BMI score will reach 28.5 kg/m^2, 30.16 kg/m^2 in 2050, 32.6 kg/m^2 in 2080 and 34.2 kg/m^2 in 2100.

Acording to WHO data, in 2016, in Africa and in the Western Pacific regions, the average BMI score was 24 kg/m^2 for both sexes. Thus, if the trends remain stable, in 2100 the rates of obesity will also reach these areas.

Our analysis also shows that in Africa, the female population will be more affected than men by obesity. In 2030 black women living in Africa may be overweight. The maximum mean BMI for them shown in our data is 25.2 kg/m^2 for 2030 and 26.86 kg/m^2 for 2050. If the weight gain will continue with the present rates, the values of the average BMI for the black women will increase at 29.3 kg/m^2 for 2080 and 30.92 kg/m^2 for the year 2100. We identified a lower value of mean BMI in black men living in Africa. For 2030 our estimated mean BMI value is 23.1 kg/m^2. As for 2050 the average BMI score doesn't surpass the cutoff value for healthy body weight (24.1 kg/m^2). Beginning with 2080, the average BMI score will be surpassing the cutoff values for ideal weight and reaching the value of 25.6 kg/m^2, while in 2100 the our estimated score is 26.4 kg/m^2.

In the Western Pacific area until 2016, the average MBIfor both sexes was in the normal cutoff values (23.7 kg/m^2). Our predictions show that the obesity rates will be higher in the male population compared to the female population. We predicted that in 2030 the average BMI score will be 25.3 kg/m^2 for the male population. Thus, in 2050 the value might increase at 27.18 kg/m^2.

As for the year 2080, the average BMI in the Western Pacific area might pass the cutoff value of 30 kg/m^2 for obesity. Also, for the year 2100, we determined an average BMI value of 31.87 kg/m^2 for men. For the women living in this area, the estimated average BMI value for 2030 is 24.27 kg/m^2. Starting with the year 2050, the mean BMI value might reach overweight cutoffs with a 25.52 kg/m^2 value, 27.4 kg/m^2 for 2080 and 28.5 kg/m^2 for 2100.

Strengths and Limitations

Strengths: New perspective on excess weight and obesity until 2100, in comparison with the existing studies and meta-analysis in the field. Limitations: There are a lot of variables which may affect the quality of the study including other BMI classifications for the Asian and Indian populations. Also, sociologic, demographic, and economic characteristics of individuals are associated with misreporting of height and weight. This may indicate that the real average BMI scores may be higher than those studied. Also the differences in reporting the BMI may

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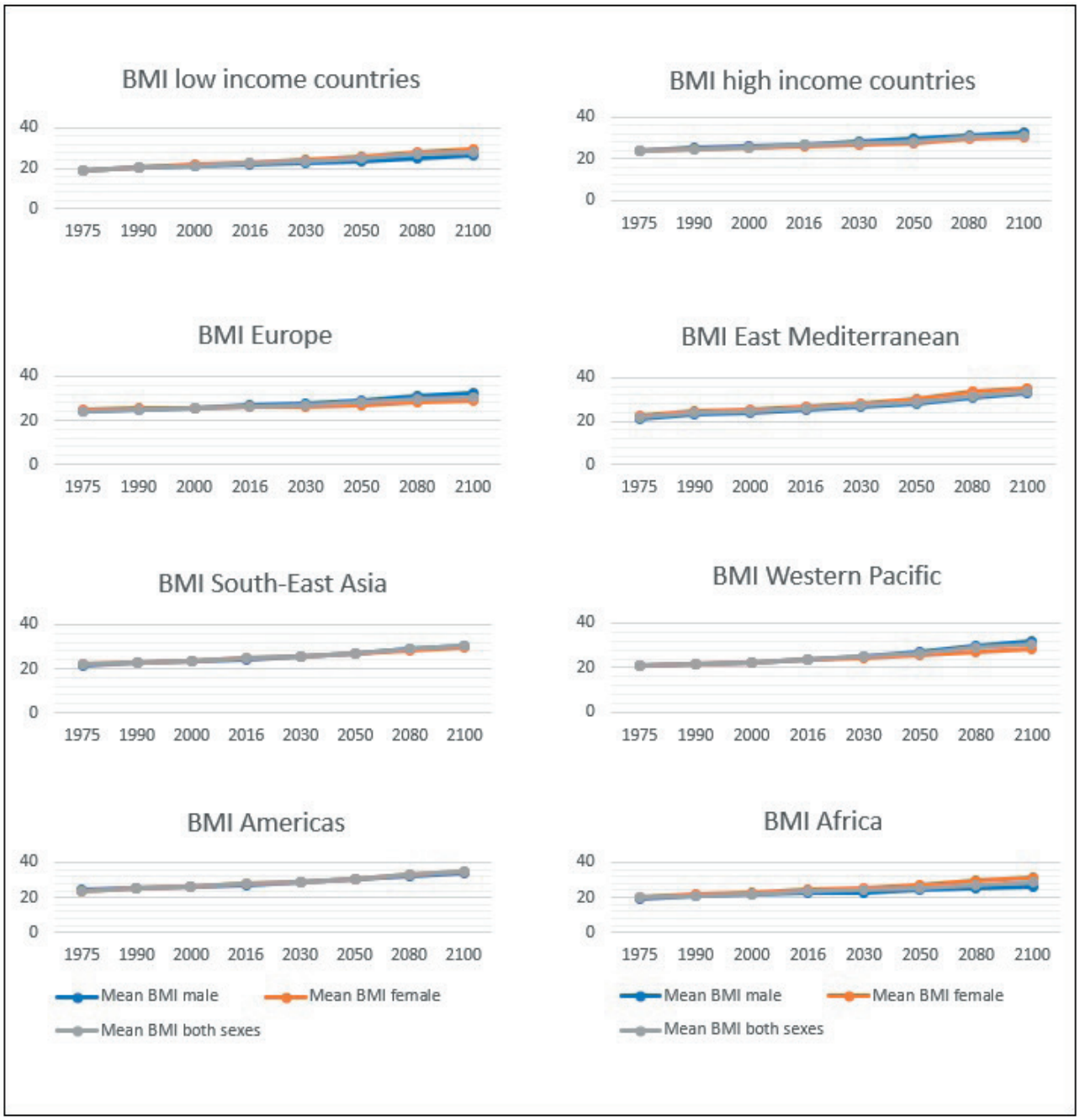

Figure 2: Mean BMI (own calculations using WHO data). Source: WHO data [3].

be affected by characteristics such as income inequality and the education level. Based on our results, future studies on obesity and the regional drivers and differences are needed.

Discussions

Little is known about the anthropometric measures and the relationship with the contextual environment in which individuals live, including social, demographic, and economic determinants.

Individual factors associated with weight gain in the general population may be avoided, thus in order to stop the further expansion of the obesity pandemic, the individual control of the main obesogenic risk factors (unhealthy diet, low level of physical activity/sedentarism) without visible obesity interventions at the community level, such as active decisions, involvement and

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coordinated efforts of local authorities to improve the local environment may be insufficient.

Conclusions

Obesity is nowadays a leading concern and a huge responsibility for the health systems worldwide. The public sector, along with the civil society and also the private sector play a key role in shaping a new paradigm to benefit society. In order to tackle the obesity pandemic there is an urgent need to find an effective perspective in building health through healthy behaviors, healthy lifestyle, food security, healthy nutritional transition, not only by providing access to healthier choices, but also by encouraging people to make those healthy choices. A sustained focus on wellbeing education, on physical activity opportunities and initiatives for healthy behavior may improve health outcomes at the population level. Additional studies are needed in order to establish the precise causality in this field and provide accurate recommendations in order to tackle obesity pandemics.

Conflict of Interest

The authors declare no conflict of interest.

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Case Report

A not so common syndrome in Europe – Hirata disease

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Abstract

Insulin autoimmune syndrome (IAS) known as Hirata disease, is a rare cause of hyperinsulinemic hypoglycemia, characterised by recurrent spontaneous postprandial hypoglycemia with elevated insulin levels. It is defined by the presence of high titres of insulin auto-antibodies, with no prior exposure to exogenous insulin and no pathological abnormalities of the pancreatic islets. A 73-year-old Caucasian woman presented with one year history of intermittent hypoglycemia episodes, which had gradually worsened in the past two weeks. Biochemical measurements showed remarkably high fasting insulinemia with levels >1000 uUi/ml and post prandial plasma glucose levels (PG) between 40 and 32 mg/dl, glycated hemoglobin concentration was 5.8 % (pre-diabetes) and the abdominal computer tomography (CT) did not show abnormalities. The 72 hours fasting test was negative. Four hours after mixed meal, the patient developed hypoglycemia with glucose levels (PG) of 34 mg/dL. Fasting insulin levels were 495 Ui/l and insulin autoantibodies (IAA) were positive 1900 u/ml (normal range <0.4) leading to the diagnosis of Hirata disease. **Conclusion:** We report a case of spontaneous postprandial hypoglycemic episodes with highly elevated levels of insulin and insulin auto-antibodies (Hirata disease) in a Caucasian patient.

Keywords: Hirata disease, hyperinsulinemia, hypoglycemia, autoimmune, IAS.

Introduction

Insulin autoimmune syndrome (IAS) known as Hirata disease is a rare cause of hyperinsulinemic hypoglycemia, characterized by recurrent spontaneous postprandial fall in blood glucose with elevated insulin levels. It is defined by the presence of high titres of insulin auto-antibodies, with no prior exposure to exogenous insulin and no pathological abnormalities of the pancreatic islets [1]. More commonly seen in adults than in children, without gender predominance and a mean age of diagnosis of 60-years-old.

It mostly appears in the presence of the human leukocyte antigen (HLA)-DR4 and can be triggered by exposure to drugs containing sulfhydryl group, viruses acting like super-antigens or can appear with no apparent cause [2–4]

Case Report

We admitted a 73-year-old Caucasian woman with one year history of intermittent hypoglycemia episodes, gradually worsened in the past two weeks. Medical history was significant for hypertension, vitiligo, and essential tremortreated with beta-blockers and pramiracetam. The patient had no personal or familial history of diabetes mellitus and no evidence for use of oral antidiabetic medication, exogenous administration of insulin, bariatric surgery, or intensive physical exercise. She denied any history of alcoholism or smoking.

Prior to our admission, the patient was hospitalized in another hospital, where blood tests showed remarkably highfasting insulinemia with levels >1000 uUi/ml (normal range 1.9–23uUi/ml) and postprandial venous PG

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showed levels between 40 and 32 mg/dl, glycated hemoglobin concentration was 5.8% (pre-diabetes), complete blood count showed normocytic anemia, mild leucocytosis, and no other abnormalities were noticed. An abdominal computer tomography (CT) scan was performed to determine the cause of spontaneous hypoglycemia. The CT scan showed no abnormalities, thus excluding a potential insulinoma.

On examination, the patient appeared alert and oriented to person and time. She had normal vital signs, with no physical and neurological anomalous findings. Her body mass index (BMI) was 28 kg/m^2. Biochemical measurements showed normal fasting glycemia (92 mg/dl) and high fasting insulinemia 495 uUi/ml (normal range 1.9–23uUi/ml).

We performed a 72 hours fasting test, which was negative as the patient did not develop hypoglycemic symptoms, therefore excluding insulinoma and other causes of fasting hypoglycemia. During the test PG ranged from 92–66 mg/dl, with gradually increasing levels of ketone bodies in serum (finger-prick testing for beta-hydroxybutyrate), showing a physiological response to fasting. After the fasting test, four hours after a meal, the patient did develop hypoglycemia. We performed blood tests during the episode and the results showed PG of 34 mg/dL with an abnormal elevated insulin level >1000 Ui/l .

Taking into consideration the postprandial hypoglycemia with extremely elevated levels of serum insulin and also the negative 72 hours fasting test, negative abdominal CT scan and ultrasonography for insulinoma, two possible diagnoses remained :1) pre-type 2 diabetes state with insulin resistance and functional hypoglycemia and 2) autoimmune insulin syndrome also know as Hirata's disease. The insulin autoantibodies (IAA) resulted positive 1900 u/ml (normal range <0.4) and the anti-insulin receptor antibodies (AIRA) were negative. These results directed us towards the diagnosis of Hirata's disease. As it is cited in the literature, Hirata's disease is known to be associated with hematological and autoimmune diseases, especially monoclonal gammopathy of undetermined significance (MGUS) so we investigated for both. Protein electrophoresis and immunoelectrophoresis came back negative for MGUS. It is to be noted that the patient reported being affected by vitiligo, an autoimmune condition of the skin.

For this patient with pre-diabetes and positive IAA we considered additional anti islet cell antibodies test: islet tyrosine phosphatase 2 (IA2) and glutamic acid decarboxylase(GAD) auto antibodies which resulted negative. Also post prandial functional hypoglycemia was never reported, in our knowledge in pre clinical type 1 diabetes.

Hirata's disease responds to the treatment of the underlying pathology and, when idiopathic, tends to be auto limited. In our patient we started a specific diet based on 6 meals per day, with reduction of carbohydrates, especially rapidly absorbable (160 g carbohydrates per day), moderate in fat, and high in protein (70 g/day protein). It was indicated that all meals contain protein and high levels of fibres and to avoid highly concentrated carbohydrates. Another aspect that was taken into consideration as a target for treatment was the insulin resistance due to the metabolic syndrome. Consequently, we decided to prescribe 500 mg of metformin, two-times a day, with up-titration to 1000 mg two-times per day. She received additional treatment with angiotensin-converting enzyme, beta-blockers and statin. The patient was discharged on day 8 of admission.

Given that the patient did not have any other new episodes of hypoglycemia after the beginning of diet and treatment, we considered the prognosis and the evolution of the disease favorable. The patient was re-evaluated at six months and showed some minor intentional weight loss, a glycated hemoglobin of 5.6%, no hypoglycemia episodes, no anemia or other abnormalities of the blood work.

Discussion

Insulin autoantibody syndrome (IAS), is a rare syndrome, firstly discovered in 1970 by Yukimasa Hirata et al. as a cause of postprandial hyperinsulinemichypoglycemic episodes [5–8]. Since then, approximately 400 cases have been reported.[9]Most of the cases, roughly 90% of them, occurred in the Japanese population. A

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strong connection between IAS and the presence of the human leukocyte antigen (HLA)-DR4 has been discovered, being the third leading cause of spontaneous hypoglycemic episodes, after insulinoma and extra pancreatic neoplasia in Japan [3,4,6]. The age of onset is 60–70 years, without any certain gender predilection [5]. Many of the patients, approximately 80–85% of them, have other autoimmune disease or hematological disorders, such as rheumatoid arthritis, Graves disease, systemic lupus erythematosus, chronic hepatitis or vasculitis, monoclonal gammopathy or multiple myeloma, with the last two described in the Caucasian population [3, 10]. IAA can appear spontaneously or can be triggered by prior exposure to certain drugs containing sulfhydryl groups, frequently by anti-thyroid drugs (ATD) mainly by methimazole [11] but also by propylthiouracil and carbimazole and by dietary supplements containing alpha lipoic acid used in diabetic neuropathy [12], anti-aging supplements, polycystic ovary syndrome. Viruses acting like super-antigens(rubella, coxsackie B, influenza, mumps, hepatitis C) can also be a trigger. [2, 3, 11, 13]. In the case of drug induced IAS, the clinical manifestations of the disease begin following the 4–6 weeks after exposure to certain drugs mentioned above, but there are some cases in literature in which the clinical manifestation started even after years [2].

The main characteristic is hypoglycemia and, depending upon its severity, it can be accompanied by autonomic symptoms (hunger, sweating, tremor, palpitation, paresthesia, anxiety) and neuroglycopenic symptoms (fatigue, seizures, loss of consciousness) [2, 3]. In a healthy individual, symptoms start to appear at glucose levels below 55 mg/dl but in patients suffering from IAS, the limit is lower. Postprandial hypoglycemia is due to the mechanism of the appearance of IAS. The core of IAS is the presence of the circulating insulin autoantibodies, mainly the IgG subtype, but there are also some cases with IgA and IgM, making it harder to diagnose because most of the kits only identify IgG. Polyethylene glycol (PEG) test should be considered as a test that can identify any type of Ig [3, 10, 14]. Insulin autoantibodies (IAA) have a high capacity and low affinity of binding insulin leading to hypoglycemic episodes related with the insulin peaks after a meal, explaining why it is important to understand the timing of the episodes, unlike insulinoma where the 73% of the patients have fasting hypoglycemia [15, 16].

The pathogenic mechanism of hypoglycemia is not yet clearly understood [17]. It is believed that after food intake, the auto-antibody binds immediately to insulin, leading to postprandial hyperglycemia. The insulin is later released by the dissociation of the antibody-insulin complex, causing hypoglycemia [5, 17, 18].

Literature cases of insulin autoantibodies (IAA) related with exogenous administration of insulin in DM type 1, noticing a milder hypoglycemia due to the low capacity and high affinity of binding insulin are worth mentioning, here [2].

The laboratory tests showed remarkably increased insulin levels, much higher than the levels found in insulinoma. C-peptide and proinsulin levels tend to be higher or to remain at normal levels. A criterion for diagnosis can be the insulin to C-peptide ratio, a normal range is lower than 1, even though they are co-secreted by the pancreatic B-cells in equimolar proportion, explained by the half-life of insulin (5–10 min) and half-life of C-peptide (30–35 minute), the latter one has a slow metabolism process through the kidneys compared to the rapid metabolism pathway of the liver. In IAS the ratio is >1 because of the formation of the antibody- insulin complex causing the delay in the metabolization of insulin.[3, 16, 19]. Glycated hemoglobin levels can be variable, from normal to high values, depending on the severity and frequency of the hypoglycemic episodes [2, 3]. *The gold standard* to confirm the diagnosis of IAS is the measurement of the insulin autoantibodies (IAA).

Most of the patients have a spontaneous remission in one to three months after the first episode [1, 20]. The prevention of the hypoglycemic episodes mainly consists of the dietary approach, where the patient is advised to have frequent meals and to avoid the intake of sweets, sugar and to frequently monitor glucose levels. If the dietary regimen is not enough to prevent the hypoglycemic episodes, the second approach is the use of high dose corticosteroids. Also, an immunosuppressive therapy, such as

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azathioprine and rituximab, can be taken into consideration in case of persistency of the disease which demonstrated a high rate of success. When the pharmacological therapy is not effective, plasmapheresis can be tried [2].

Conclusion

We report a case of spontaneous postprandial hypoglycemia episodes with highly elevated levels of insulinemia and insulin autoantibodies, leading us to the rare diagnosis of Hirata disease in a Caucasian patient. In this case, the dietary approach and treatment with metformin proved to be successful.

Conflict of Interest

The authors declare no conflict of interest.

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Case Report

Metabolic changes of lipids in patient with subclinical hypothyroidism

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Abstract

Background and Aims: the effect of subclinical hypothyroidism on the dynamics of lipid spectrum during lipid-tolerance test was studied. Subclinical hypothyroidism (SH) is the earliest thyroid dysfunction and is the most common. However, data on the presence of dyslipidemia in subclinical hypothyroidism are controversial. The aim of this study was the early detection of lipid metabolism disorders in patients with subclinical hypothyroidism on the basis of lipid-tolerance testing. **Materials and Methods:** the study involved 96 people. The main group included 37 patients with subclinical hypothyroidism, but seven of them had fasting hypercholesterolemia, dyslipidemia, and they were excluded from further study. Thus, 30 patients with SH formed the main group 1. Two comparison groups were presented by 59 comparisons by main characteristics (age, sex, exclusion criteria) of individuals without thyroid pathology (group 2) - 30 people, and with overt hypothyroidism (group 3) - 29 people. An oral fat tolerance test was used to evaluate postprandial lipemia. **Results and Conclusions:** As a result of the study, data were obtained according to which fat load stimulated the development of different levels of postprandial hyperlipidemia, depending on the thyroid status of patients. Patients with subclinical hypothyroidism had postprandial hypertriglyceridemia, which was combined with an increase in low-density lipoprotein levels and a decrease in high-density lipoprotein levels. The proposed method allows the detection of early disorders of lipid metabolism in patients with subclinical hypothyroidism.

Keywords: Lipidotolerance test, postprandial hypertriglyceridemia, subclinical hypothyroidism.

Background

According to a large-scale meta-analysis of N. Rodondi, which involved more than 55,000 patients, a correlation of cardiovascular morbidity (CVM) with thyroid-stimulating hormone (TSH) was found. A significant increase in the risk of CVM was established at TSH> 7 mU/l [1–3]. According to WHO data, hypercholesterolemia in patients with hypothyroidism is one of the significant manifestations of the disease, and is found in 93.4% of patients. As in patients with ischemic heart disease, hypertriglyceridemia and dyslipoproteinemia are observed in patients with hypothyroidism [1-–3]. Along with the increase in total cholesterol in patients with hypothyroidism, there is a decrease in high-density cholesterol-lipoprotein (HDL-lipoprotein) and an increase in low-density lipoprotein (LDL-lipoprotein) cholesterol, while decrease in LDL/HDL ratio.

Thyroid hormones affect the synthesis of lipids, but to a much greater extent

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the processes of their degradation. They are involved in the utilization of fats, mobilization of triglycerides from adipose tissue through activation of enzymes, liver lipase (LL), lecithin-cholesterol-acetyltransferase (LCAT) and cholesterol-ether transport protein HETP [1–3]. LL participates in the processes of remodeling of various lipoproteins, LCAT esterifies free cholesterol, HETP mediates the exchange of cholesterol esters between lipoproteins and is a key factor in reverse cholesterol transport. If long-term hypothyroidism persists, there may be a significant decrease in HETP and LL activity [3–5].

In the study of the processes of atherogenesis, much attention is paid to the influence of oxidized forms of LDL cholesterol on the formation of atherosclerotic plaque. Increasing their level is an important marker of the activity of the atherosclerotic process [5]. Oxidized LDL cholesterols have been found to be crucial in endothelial damage, as they stimulate lipid migration into the subendothelial space and their capture by macrophages leading to the formation of foam cells [6–8]. In addition, under conditions of thyroid hormone deficiency, there is a decrease in the number of LDL receptors in the liver, which leads to a decrease in the excretion of cholesterol by hepatocytes and, as a consequence, an increase in the level of LDL and HDL [8]. Thus, a decrease in thyroid function contributes to the development of atherosclerosis. The level of hypercholesterolemia in patients with hypothyroidism correlates with the severity of hypothyroidism, and therefore the highest cholesterol figures are observed in patients with myxedema [8].

Subclinical hypothyroidism (SH) is the earliest thyroid dysfunction and is the most common. However, data on the presence of dyslipidemia in subclinical hypothyroidism are controversial [3–5].

Lipidogram does not always allow an objective assessment of cardiovascular risk, as it is known that in about one third of patients with clinically pronounced atherosclerosis, including coronary arteries (CA), indicators of atherogenic fractions of lipids and lipoproteins (LP) are within the normal values [7–9]. However, in this group of patients there are certain disorders of the blood lipid transfer system (LTS). In normal clinical practice, the effect of prandial fats on lipid metabolism is not studied, as the effects of exogenous fats on lipid spectrum (LS) values are not tested. Post-prandial lipemia, which is defined as the degree and duration of the increase in triglyceride (TG) levels, is generally known to occur after the consumption of fatty foods.

According to the studies [7–9], exogenous fats which cause the phenomenon of postprandial hyperlipemia (PPH), have the most adverse atherogenic effect. In the postprandial period, absorption of chylomicrons and LDL by the arterial wall occurs [9]. Postprandial hyperlipidemia lasts for several hours after each meal, so the person is in this state for most of the day [9–13]. Recent studies have confirmed the atherogenic nature of postprandial dyslipidemia as an independent risk factor for cardiovascular disease. Data on the state of lipid metabolism in subclinical hypothyroidism are controversial, since studies of lipidogram were performed on an empty stomach, namely postprandial lipidemia and the effect of fat loading in patients with subclinical hypothyroidism was not studied [13–15].

Aim of this study was the early detection of lipid metabolism disorders in patients with subclinical hypothyroidism on the basis of lipid-tolerance testing.

Materials and Methods

The study conducted at the Department of Endocrinology of the State Establishment "Dnipropetrovsk Medical Academy of Health Ministry of Ukraine" involved 96 people. The criteria for inclusion in the study were: confirmed diagnosis of SH (twice with an interval of three months detecting TSH level> 4.0 μME/ml at normal fT4 level - 12–22 pmol/l); age of patients under 45; voluntary consent to participate in the study. Exclusion criteria were: presence of cardiovascular pathology (ischemic heart disease, hypertension); chronic liver and kidney diseases with impaired function; oncological, rheumatic diseases; autoimmune diseases (except Hashimoto's disease); diabetes; hypertension; smoking; taking hypolipidemic drugs; pregnancy. Thyrotropic hormone (TSH) and free thyroxine (fT4) fraction

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were determined as screening. The etiologic factor of hypothyroidism was predominantly autoimmune thyroiditis (elevated antibody titer to thyroid peroxidase was detected in 48 patients out of 59 patients with hypothyroid status of varying severity). The main group included 37 patients with subclinical hypothyroidism, but seven of them had fasting hypercholesterolemia, dyslipidemia, and they were excluded from further study. Thus, 30 patients with SH formed the main group 1. Two comparison groups were presented by 59 comparisons by main characteristics (age, sex, exclusion criteria) of individuals without thyroid pathology (group 2), 30 people, and with overt hypothyroidism (group 3), 29 people.

To exclude atherosclerotic lesions of arteries, a color duplex scan of the brachiocephalic arteries was performed with calculation of the intima-media ratio (mean 0.57 mm ± 0.02 was obtained) and a treadmill test during which the ischemic type of reaction was excluded.

An oral fat tolerance test was used to evaluate postprandial lipemia using the J. Patch method, according to which a standard fat diet was carried out at the rate of 65 g of fat per 1 m^2 of body surface. 72.5% butter was used as the fat source, along with 50 g of white bread. Blood samples were taken on an empty stomach and three hours after fat load. Patients did not take food during the study. The following parameters were investigated: total cholesterol (TC), triglycerides (TG), and low-density lipoproteins (LDL-lipoproteins).

To determine the level of cholesterol and its fractions, the enzymatic colorimetric direct method was used, using reagents "HUMAN", Germany, on a SAPPHIRE 400 apparatus.

Statistical processing of the study materials was performed using the STATISTICA v.6.1 software package (Statsoft Inc., USA) (license number AGAR909E415822FA). Taking into account the law of quantitative data distribution (Liliefors and Shapiro-Wilk criteria), parametric and non-parametric methods were used. In the case of the normal distribution law, the statistical characteristics are represented as arithmetic mean (M), standard error of the mean (m), 95% confidence interval for the mean (95% CI), in other cases the values of median (Me) and interquartile variance are given [25%; 75%]. Comparisons of statistical characteristics in the different groups and in the dynamics of the observation were performed using the Student's t test for paired (T) and independent (t) samples, Mann-Whitney (U) and Wilcoxon (W) criteria; multiple comparison by ANOVA (F) and Kruskall-Wallis (H) analysis of variance; the likelihood of differences in the relative indices was estimated by Pearson's Chi-square test ($\chi 2$). Differences were considered statistically significant at $p<0.05$.

Results and Discussion

The main characteristics of the examined patients at the onset of the study are shown in Table 1. All selected study groups were statistically comparable ($p > 0.05$) by age and gender of patients, as well as BMI that met the criteria (18–24.9 kg/m^2). At the same time, the groups significantly ($p<0.001$) differed in the levels of TSH, fT4, fT3 and antibodies to thyroperoxidase (Ab-TPO). In particular, the TSH level in the serum of patients with SH was 4.2-times higher than in patients without thyroid pathology ($p<0.001$), but was 12.8-times reduced relative to patients with overt hypothyroidism ($p < 0.001$). The production of fT4, fT3 hormones in the blood of group one patients was normal ($p > 0.05$) and exceeded the same parameters in group 3 by 2.3 and 1.9-times, respectively ($p<0.001$).

The most specific marker of lipid tolerance disorder is the dynamics of the level of TG and LDL in three and six hours after fat loading [15–18]. In our study, we used the determination of postprandial lipid metabolism in three hours as this point is as informative as possible. In the first two hours after nutrition loading, the phase of early postprandial physiological hyperlipidemia continues. By the three-hour mark in healthy subjects without lipid metabolism, this phase is fully completed, which gives grounds for evaluation and comparison in patients with subclinical hypothyroidism.

Data on the results of the study of fasting lipidgram indices and after lipid-tolerance test are presented in table 2 and figure 1, 2, 3.

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Table 1: Main characteristics of the examined patients at the onset of the study.

Characteristics	Group 1 – SH (n = 30)	Group 2 – without TG pathology (n = 30)	Group 3 – overt (n = 30) hypothyroidism	Significance of difference between groups as a whole*
Age, years, M±m	32.4 ± 1.6	31.8 ± 1.6	33.2 ± 1.5	F = 0.20, p > 0.05
Gender, n/ %:				
male	8/26.7	11/36.7	9/30.0	χ^2 = 0.73, p > 0.05
female	22/ 73.3	19/ 63.3	21/ 70.0	
BMI, kg/m^2, M±m	20.4 ± 0.5	21.2 ± 0.6	22.1 ± 0.7	F = 2.28, p > 0.05
TSH, μME /ml, M±m	7.43 ± 0.41 *p2, p3*	1.77 ± 0.09 *p1, p3*	95.18 ± 6.69 *p1, p2*	F = 183.2, p < 0.001
fT4, pmol/l, M±m	16.65 ± 0.57 *p3*	15.82 ± 0.53 *p3*	7.14 ± 0.55 *p1, p2*	F = 91.2, p < 0.001
fT3, nmol/l, M±m	2.04 ± 0.10 *p3*	2.20 ± 0.11 *p3*	1.10 ± 0.01 *p1, p2*	F = 45.5, p < 0.001
Antibodies to TPO, ME/ml, Me [25%;75%]	1426.6 [565.5; 2456.8] *p2*	15.5 [8.1; 27.1] *p1, p3*	1079.7 [544.3; 2291.6] *p2*	H = 55.8, p < 0.001

Notes: *p1, p2, p3* – *p* < 0.001 compared to the corresponding group 1,2,3; * - significance of differences between groups as a whole by one-way ANOVA (F), Kruskall-Wallis (H), Pearson Chi-square (χ2).

From the data in table 2 it is seen that in 3 hours there was a significant increase in levels of total cholesterol, triglycerides, and LDL cholesterol in patients with subclinical hypothyroidism (group 1) and group with overt hypothyroidism (group 3) at *p*<0,001. Thus, in patients with SH and normal fasting lipidogram after a load test a long-term postprandial hypercholesterolemia is noted, characterized by a probable (*p*<0.001) increase in the level of TC on average by 0.67 mmol/L or by 14.6%, TH – by 0.89 mmol/l (by 52.0%), the level of LDL cholesterol - by 1.28 mmol/L (by 50.2%).

Similar pronounced changes in lipidogram three hours after load were observed in overt hypothyroidism: the average level of TC was significantly (*p*<0.001) increased by 0.58 mmol/L, i.e. by 11.4%, TH level - by 0.73 mmol/L (by 31.7%), the content of LDL cholesterol - by 0.89 mmol/L (by 24.3%).

In the control group in the euthyroid status there were no statistically significant changes in the indices of the lipidogram, either fasting or three hours after fat load (*p*> 0.05).

Comparative analysis of lipid-tolerance test results between study groups showed that statistically comparable levels of TC and its fraction (LDL-cholesterol) in the serum of patients of the 1st and 2nd groups obtained on an empty stomach (*p*> 0.05) showed a significant difference of indices 3 hours after fat load (figure. 1, 2). In patients with SH index of TC was higher by 14.1%, and the level of LDL cholesterol - by 50.2% than in the group of patients with euthyroid status (*p*<0.001).

In the group of patients with overt hypothyroidism, lipidogram values were significantly higher than in patients with SH and euthyroid status at all stages of the study at *p* < 0.001 (figure 1, 2, 3).

Thus, at this stage of the study, it was demonstrated that the consumption of dietary fats in individuals with euthyroid status and in patients with subclinical hypothyroidism stimulated the development of different levels and duration of hyperlipemia by increasing fraction of TG-rich LP. This is likely to be due to a decrease in liver lipase activity and a cholesterol-ether transport protein under conditions of the least thyroid hormone deficiency, and a parallel decrease in the number of LDL receptors in the liver.

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Table 2: Averaged TC, TG, LDL cholesterol according to lipid-tolerance test (M ± m).

Study groups	TC, mmol/L		p	TG, mmol/L		p	LDL cholesterol, mmol/L		p
	0*	3*		0*	3*		0*	3*	
Group 1 – SH (n=30)	4.58 ± 0.09	5.25 ± 0.08	<0.001	1.71 ± 0.01	2.60 ± 0,03	<0.001	2.55 ± 0.01	3.83 ± 0.04	<0.001
Group 2 – without TG pathology (n=30)	4.56 ± 0.10	4.60 ± 0.09	0.817	1.22 ± 0.05	1.30 ± 0,05	0.105	2.54 ± 0.01	2.55 ± 0.01	0.107
Group 3 – overt hypothyroidism (n=30)	5.11 ± 0.06	5.69 ± 0.06	<0.001	2.30 ± 0.06	3.03 ± 0,03	<0.001	3.66 ± 0.02	4.55 ± 0.04	<0.001

Notes: *time of blood taking, hours; p - level of significance of differences between indices before and after nutrition load (Student's T-test).

In some patients with high TSH, no clinical or laboratory evidence of hypothyroidism is observed. In addition, some ethnic groups have a genetically determined elevated TSH, which is not accompanied by a thyroid disorder. The lipidogram and lipid load test are cost-effective and simple laboratory studies to further evaluate cardiovascular risks in patients with hypothyroidism of varying severity and to make a clinical decision on adjustment of the corrective dosage of levothyroxine, the target level of TSH.

Conclusions

1. In patients of group 1 and 2 the mean levels of total cholesterol and LDL cholesterol were statistically comparable and in 3 hours after the fat load in patients of group 2 they remained unchanged, but probably increased by 14.6% and 50.2% in those of group 1. Thus, dyslipidemia in the postprandial period in individuals without additional risk factors was only found in individuals with thyroid disorders.
2. Subclinical hypothyroidism leads to lipid metabolism disorders, which are detected by the method of fat load test, and is a risk factor for the development of cardiovascular pathology resulted from long-term postprandial dyslipidemia.
3. Fat load test can be used as a marker of lipid metabolism disorder in patients with subclinical hypothyroidism and may be performed for early detection of dyslipidemia and timely correction.

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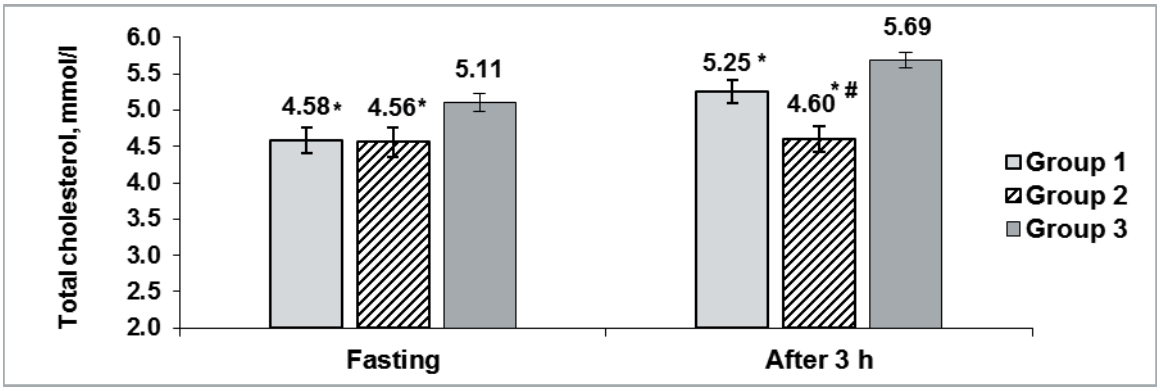

Figure 1: Average levels (M, 95% CI) of total fasting cholesterol and in three hours after fat load in groups 1, 2 and 3: * – $p < 0{,}001$ compared to group 3; # – $p < 0.001$ compared to group 1 (Student's t-test).

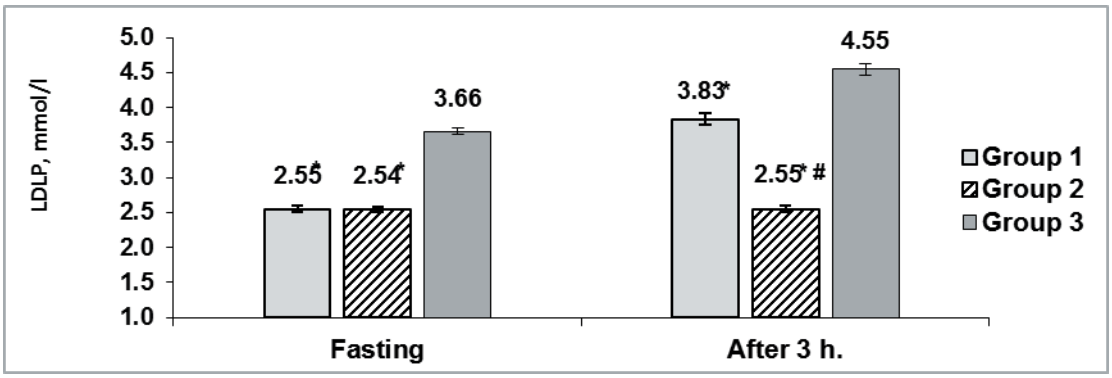

Figure 2: Average levels (M, 95% CI) of fasting LDL cholesterol and in three hours after fat load in groups 1, 2 and 3: * – $p < 0{,}001$ compared to group 3; # – $p < 0.001$ compared to group 1 (Student's t-test).

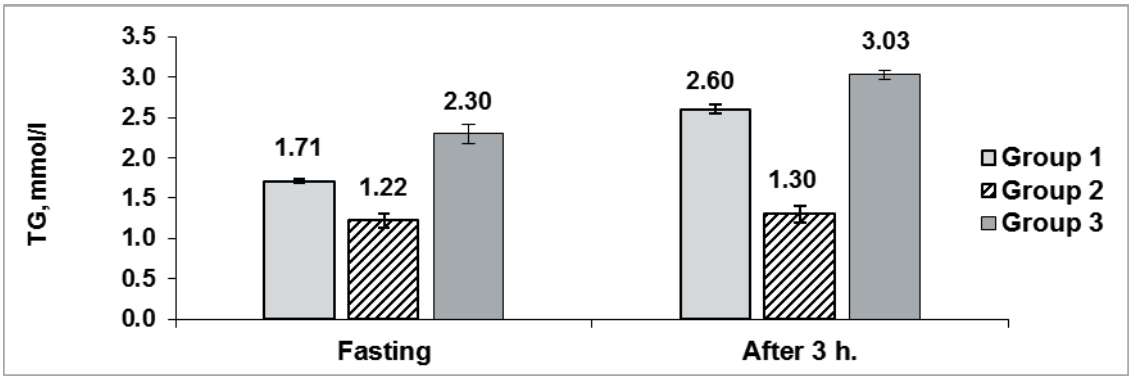

Figure 3: Average levels (M, 95% CI) of fasting triglycerides and in three hours after fat load in groups 1, 2 and 3: $p < 0.001$ for all comparisons between groups (Student's t-test).

«Laboratory of the Medical Diagnostic Center of the Medical Academy». The authors are grateful and offer deep appreciation to Dr. Irina Gubar and Dr. Yevgen Martsynik for the advice and valuable comments given while working on this article.

Conflict of Interest

The authors declare no conflict of interest.

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Case Report

New-onset type 1 diabetes mellitus in an adolescent boy with glucose-6-phosphate dehydrogenase deficiency

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Abstract

Background and Aims: Glucose-6-phosphate dehydrogenase (G6PD) deficiency and diabetes mellitus could aggravate each other when they co-exist.The aim of this report is to raise the awareness of clinicians regarding the possibility of co-existence of diabetes mellitus and G6PD deficiency in adolescents with an additional history of passage of dark-colored urine. **Case Report:** We report a case of a 16-year-old Nigerian boy with newly-diagnosed type 1 diabetes mellitus (T1DM) co-existing with glucose-6-phosphate dehydrogenase deficiency which manifested as hemoglobinuria. **Conclusion:** The index case suggests that in the initial period of T1DM, even without ketoacidosis, patients with G6PD deficiency are predisposed to hemolysis, manifesting as hemoglobinuria. Additionally, patients with T1DM, presenting with hemoglobunuria should be investigated for G6PD deficiency.

Keywords: Diabetes mellitus, glucose 6 phosphate dehydrogenase, hemoglobinuria, Nigeria.

Introduction

Glucose-6-phosphate dehydrogenase (G6PD) is a cytoplasmic enzyme that catalyzes the first step in the production of reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) in the pentose phosphate pathway. G6PD deficiency is an X-linked recessively inherited enzyme defect and the defect gene has been mapped at Xq28 [1]. The World Health Organization has classified G6PD deficiency into five variants, classes I to V, based on level of enzyme activity and the severity of the hemolytic episode and its clinical manifestations. Class-I variant, residual enzyme activity less than 10%, is associated with chronic hemolysis. In the Mediterranean basin, it is usually the class II variant with residual enzyme activity less than 10% with intermittent acute haemolysis. Class III deficiency has moderate residual enzyme activity (10–60%) with intermittent acute haemolysis and is due to gene G6PD A (African variant). Classes IV and V are of no clinical significance [2]. The two most common mutations of G6PD are the G6PD Mediterranean and G6PD African.

In the red blood cells, defense against oxidative damage is heavily dependent on G6PD, which is the only source of NADPH [3]. This protection is achieved via maintenance of intracellular pool of reduced gluthathione. Majority of individuals are asymptomatic and do not have hemolysis in the steady state. They have neither anemia, nor evidence of increased red blood cell destruction or an alteration in blood morphology [1]. Occurrence of symptoms has been associated with exposure to some drugs and food (e.g., antimalarials and fava beans), severe

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bacterial infections and diabetic ketoacidosis [1, 2, 4, 5]. The clinical manifestations of G6PD deficiency include prolonged neonatal jaundice and hemolytic anaemia, which may be acute or chronic. The reported prevalence of G6PD deficiency among Nigerian children is 15.3% [6].

The results of some studies suggest that G6PD deficiency is a risk factor for diabetes mellitus (DM) [7, 8]. Additionally, diabetic ketoacidosis may trigger hemolysis in G6PD-deficient individuals [4, 5]. Diabetes mellitus (DM) is characterized by high blood glucose level which is a major source of free radicals through several mechanisms [9]. Although hamolysis has been reported in newly-diagnosed type 1 diabetes (T1DM), it is uncommon [10, 11]. In European literature, majority of the reports on the subject focus on the Mediterranean variant of G6PD deficiency [4, 5, 12]. However, the African variant has been shown to trigger hemolysis in diabetic ketoacidosis [13].

Case Report

We report a case of a 16-year-old Nigerian boy who presented with fever and occasional vomiting, polyuria, weight loss, and generalized weakness all of one week duration. Four days after his parents administered an antimalarial (artemeter-lumefanthrine) procured from a patent medicine shop, he started passing dark-colored urine. He has had two similar episodes in the past following fever and administration of an antimalarial. This change in urine color prompted his presentation to a private clinic where random blood glucose was performed and found to be elevated (247 mg/dl). HbA1C was elevated by 7.6%. There was a positive family history of DM. His maternal grandmother reportedly had occasional episodes of passage of dark-colored urine. However, there was no similar history in maternal uncles. History of neonatal jaundice was negative. Physical examination revealed moderate dehydration, bilateral pitting pedal edema, evidence of weight loss, and blood pressure of 130/70 mmHg (90th centile for age, gender, and height). There was no jaundice. Other physical examinations were unremarkable. A provisional diagnosis of T1DM with G6PD deficiency was made. Acute glomerulonephritis and urinary tract infection were also considered. G6PD assay was markedly reduced at 1.047 U/gHb (reference interval 7.9–16.3g/Hb), representing 8.7% of mean normal enzyme activity. Full blood count and serum E/U/Cr were essentially normal. The cold agglutinin test and Coomb's test were negative. The hemoglobin concentration was 10.7g/dl. Urine microscopy did not show red blood cells (RBC) or RBC casts. Peripheral blood smear revealed bite cells, Heinz bodies and spherocytes. Serum bilirubin (both total and direct) was slightly elevated. The other laboratory findings are summarized in table 1.

The antimalarial was immediately discontinued. He was started on oral amoxicillin-clavulanic acid and subcutaneous insulin. The patient and the care-givers were counseled regarding G-6-PD deficiency, possible triggers, and pointers to hemolysis as well as self-care practices relating to type 1 diabetes mellitus. Following improvement in his clinical condition, he was discharged. He is being followed up in our pediatric endocrinology and hematology clinics. His last clinic visit was a few days ago with good glycemic control and no hemolytic crises.

Discussion

We describe a case of newly-diagnosed T1DM associated with hemoglobinuria/hemolysis. Additional evidence of hemolysis includes the absence of RBC or RBC casts on urine microscopy and the presence of bite cells, Heinz bodies, and spherocytes in peripheral blood smear. The passage of dark-colored urine prompted presentation to hospital where an incidental random blood glucose level check was found to be in a range suggestive of diabetes mellitus. Our patient's HbAIC concentration (7.6%) was also suggestive of DM. The relatively low HbA1C observed in our patient may be due to the simultaneous presence of G6PD deficiency. This may be explained by a reduction in average erythrocyte life span in G6PD deficiency, resulting in younger RBCs in such patients. The implication in clinical practice is that we should suspect G6PD

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Table 1: Summary of laboratory results in our patient.

Laboratory test	Results	Comments
Urine glucose	4+	Glycosuria
Urine protein	2+	Moderate proteinuria
Urine blood	+	Hemoglobinuria present
Urine microscopy	No RBC or RBC casts	Hematuria absent
Urine M/C/S	*Pseudomonas aeroginosa*	Urinary tract infection
Urine SG	1.030	High
Serum creatinine	0.6 mg/dl	Normal
Serum cholesterol	243 mg/dl	Elevated
HDL cholesterol	19 mg/dl	Low
LDL cholesterol	187 mg/dl	Elevated
Serum triglyceride	186 mg/dl	Elevated

deficiency in patients with diabetes whose HbA1C concentration is relatively low. Other laboratory results did not reveal acidosis or ketonuria, negating the diagnosis of diabetic ketoacidosis in our patient. The diagnosis of G6PD deficiency in the index case was based on low G6PD activity (representing 8.7% of mean normal enzyme activity) and the presence of evidence suggesting hemolysis/hemoglobinuria. Combined dyslipidemia was present in our patient, suggesting the need to explore the possibility of a link between G6PD deficiency and early development of dyslipidemia in adolescents with diabetes mellitus. Some researchers have demonstrated that G6PD activity was significantly lower in dyslipidemic patients with diabetes mellitus compared to their counterparts without dyslipidemia [14].

In patients with G6PD deficiency, hemolysis may occur as a result of ingestion of oxidant drugs and bacterial infections. An anti-malarial agent was administered to the patient and he also had proven urinary tract infection, both factors might have contributed to the observed hemolysis/hemoglobinuria. Our patient presented with hyperglycemia which, in itself, is capable of causing a reduction the activity of G6PD, resulting in hemolysis. Some researchers have linked the observed decrease in G6PD activity after exposure to high levels of blood glucose to both post-translational mechanisms and decreased gene expression [15]. In the index case, laboratory results did not reveal acidosis or ketonuria, negating the diagnosis of diabetic ketoacidosis in our patient. Various mechanisms have been postulated to explain the hemolysis found in newly-diagnosed T1DM without ketoacidosis. One factor that might potentially weaken the structure of the erythrocyte membrane in T1DM is the associated insulin deficiency. In normal individuals, insulin increases calcium concentration within RBC with a subsequent increase of the activity of phosphofructokinase in the glycolytic pathway. This process increases ATP production, stabilizes the membrane of a RBC, preventing its hemolysis [16]. This protective biochemical process may be compromised in T1DM. Other factors capable of precipitating hemolysis in G6PD- deficient patients are diabetic ketoacidosis and hypoglycemia [4, 5, 16], both of which were absent in the index case.

With regard to prognosis, G6PD deficiency and diabetes mellitus could aggravate each other [17]. The risk of hemolysis in patients with G6PD deficiency would be increased in case of diabetic crisis [4, 5]. Hyperglycemia in itself is known to reduce the activity of G6PD, making such a patient more prone to hemolysis [15, 18]. G6PD deficiency has been linked with increased risk for development of diabetes mellitus [8, 19, 20]. Within this context, West proposed that

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alterations in genes controlling both insulin secretion and G6PD-mediated antioxidant defenses may contribute to predisposition to DM [21]. The implication in clinical practice is that more attention should be paid to avoid severe hemolysis in the treatment of patients with G6PD deficiency, co-existing with DM.

In conclusion, the index case suggests that in the initial period of T1DM, even without ketoacidosis, patients with G6PD deficiency are predisposed to hemolysis, manifesting as hemoglobinuria. Additionally, patients with T1DM and hemoglobunuria should be investigated for G6PD deficiency.

Conflict of Interest

The authors declare no conflict of interest.

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Case Report

Type 2 diabetes in young adults, can we do more for them? – case presentation

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Abstract

Type 2 diabetes mellitus (T2DM), once considered a disease of old age, now occurs not uncommonly in children and young adults. Youth-onset type 2 diabetes is on the rise, and trends in childhood obesity only partially explain the recent appearance of a condition that was previously confined to adults. The difficulty in T2DM in young adults highlights the critical need to promote healthy lifestyle to prevent or postpone the development of T2DM in those at risk. For individuals with early onset T2DM, glycemic control must be carefully monitored and treated. We reported here a case that provides a successful management and treatment of the use of metformin, liraglutide, and most important lifestyle modifications to reduce body weight in young obese patient with poorly controlled and new diagnosed T2DM.

Keywords: lifestyle, liraglutide, obesity, Type 2 diabetes, young adults.

Introduction

We are all very well acquainted with the enormous and increasing impact of diabetes mellitus on individuals and society worldwide. The obesity pandemic has spared no age group, including young children. Type 2 diabetes mellitus (T2DM), once considered a disease of old age, sadly now occurs not uncommonly in children and young adults [1]. Youth-onset T2DM is on the rise, and trends in childhood obesity only partially explain the recent appearance of a condition that was previously confined to adults [2, 3].

The mechanism of T2DM onset in youth:

1. Development of T2DM in youth is influenced by biological and environmental variables, e.g., genetic risk, epigenetics, diet, physical activity, sex hormone production, and insulin resistance during puberty.
2. Some risk factors differentiate effects according to sex and stage of life, e.g insulin resistance is higher in females from childhood to mid-puberty, whilst it is greater in males during late puberty and adulthood [4, 5].

The largest clinical trial, Treatment Options for T2DM in Adolescents and YOUTH (TODAY study), has shown that oral agent monotherapy does not maintain durable glycemic control in approximately 50% of patients with adolescent-onset T2DM and a hemoglobin A1c (HgA1c) >6.3% in females and 5.6% in males following initial metformin monothepary predicts glycemic deterioration [6]. Thus, it is important to optimize treatment using a combination

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of pharmacological and non-pharmacologic interventions [7], with close monitoring and follow-up [8, 9]. Ideally, the care of an adolescent with T2DM should be managed by a multidisciplinary team, including an endocrinologist, nurse educator, dietitian, mental health professional, and sometimes an exercise physiologist [10, 11, 12].

The following case presentation provides a successful management and treatment of the use of metformin, liraglutide, and most important the lifestyle modifications which help to reduce body weight in young obese patients with poorly controlled and newly diagnosed T2DM.

Case Presentation

A 19-year-old obese male presented to the department of Endocrinology, 8th September City General Hospital, Skopje, for the first time with complaints of high glycaemia (30 mmol/l), felling very thirsty, often urinating and blurry vision for one month. He was diagnosed as type 1 diabetes mellitus (T1DM) 2–3 days ago in a local poly clinic and insulin therapy in four doses (basal bolus therapy) was prescribed without any improvement. He had a family history of diabetes, high blood pressure and dyslipidemia. He is a nonsmoker with no children and works in private firm.

Investigations

Initial investigations showed extremely elevated HgA1c 110.3 mmol/mol (12.2%), high glycaemia (30 mmol/l), glycosuria, elevated cholesterol (7.0 mmol/l), and triglyceride (2.8 mmol/l). His renal and liver functional tests were within normal limits. The tests for thyroid functional were also normal. Because of his weight, additional tests were made T1DM was ruled out by negative anti-islet antibody test results. He was 170 centimetar tall, 107 kg weight and his body mass index (BMI) was 37.0. Echotomography showed steatotic liver, echocardiography, and ophthalmic tests were normal.

Treatment

Based on clinical and biochemical tests, the patient was diagnosed with T2DM and rehydration with fluids and fast acting insulin in small doses was given until we achieved the desire glycemia. Because the patient was overweight and his biggest concern was his weight, he also had insulin resistance and many other additional factors, the medical team decided to start the treatment with metformin (1000 mg couple of days and after 2000 mg per day) and liraglutide with gradual titration of the dose (was started at 0.6 mg daily subcutaneously for one week and then increased to 1.2 mg daily) with additional lifestyle modifications (balancing food and physical activity). The goal of this combination was to improve glycemic control and encourage weight loss (table 1). The patient felt good, without any side effects from the therapy. As soon as we achieved glycemia at referent values his lipids status was normalized. He was discharged from our department in good condition, without any symptoms and with liraglutide 1.2 mg per day and Tbl Metformin a 2000 mg per day.

At the follow-up visit one month later, the patient denied any side effects or adverse reactions from the therapy with liraglutide and metformin and was pleased that he had lost 4 kg. He had greatly improved HgA1c 64.4 mmol/mol (8.0%) and fasting glycaemia 4.64 mmol/l. He also reported checking his blood glucose often and having glycemia in referent values.

Three months later his HgA1c was improved to 37.1 mmol/mol (5.5%), fasting glycemia 4.78 mmol/l and additional liver and kidney tests were normal. He admitted having some episodes of hypoglycemia (glycemia 3.7–4.0 mmol/l) but he said they were asymptomatic and did not require medical attention. He had lost additional 12kg and his BMI now was 31.5. He said he had more energy and felt better every day. He continued with the therapy, balancing food intake and physical activity.

At follow-up 3–4 months later, his average glucose readings were between 3.0–4.8 mmol/l. While taking liraglutide, combined with balance food and physical activity he had lost additional 12 kg and his BMI has decreased to 27.3. His HgA1c

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was 34.8 mmol/l (5%) and the other functional tests were in referent values. But he admitted having more frequent episodes of hypoglycemia, particularly after physical activity, but they did not require medical attention because after consuming carbohydrates he felt better. Because of this information we advised the patient to stop taking liraglutide and to continue only with metformin 2000 mg daily, balance food and physical activity.

At the next follow-up 5–6 months later, his average glucose reading was 5.0 mmol/l, his HgA1c was 37.3 mmol/l (5.5%), and he had lost additional 5 kg. His BMI now was 25.6 and he hadn't experienced hypoglycemic episodes for the past 5–6 months. We continued with this treatment and neither any adverse event or elevated glycemia and HgA1c had occurred thereafter.

Discussion

Metformin monotherapy provided durable glycemic control in only one part of patients, indicating that this disease can be more aggressive and rapidly progressive when onset is early in life. It is therefore important to carefully and frequently monitor these patients and intensify therapy, according to their parameters. Individualizing treatment regimens should be given consideration [7]. GLP-1 has been reported to have several functions as follows: stimulating insulin secretion, inhibiting glucagon secretion, promoting glucose production and glucose uptake in the liver, increasing glucose uptake and glycogen production in skeletal muscle, decreasing food intake for the central nerve, delay of gastric emptying, and so on [13, 14].

In our case report, we observed that the prevalence of T2DM and metabolic syndrome in the young patient was in correlation with a family history of diabetes. Moreover, young adults with a currently normal glucose tolerance, but with family history of diabetes, have higher FPG and triglyceride levels, which indicates a future risk of progression to T2DM and metabolic disorders [15]. The risk of T2DM and metabolic syndrome is greater among young adults with a family history of diabetes [3], so that's why screening and lifestyle interventions are needed [16]. In this case presentation, we showed the efficacy of liraglutide, its influence on changes in quality of life (QOL) [12], and the correlation between changes in HbA1c and body weight [9]. Liraglutide therapy decreased HbA1c level and body weight, and improved patient QOL as evidenced [17]. As expected, we observed a significant improvement in clinical parameters, reduction in weight, BMI, and HbA1c at 12 weeks after liraglutide initiation [18].

One of the elements of diabetes treatment is normalization of glucose levels, which protects the patient from the consequences of chronic hyperglycemia [19]. Change in lifestyle habits remains an important component

Table1: Patient's diabetes medication changes over time.

Reference date	Medical change	HgA1c (%) at time of change	Weight loss
Date liraglutide was added	Liraglutide 1.2 mg + metformin 2000 mg daily	12.2%	107 kg
1 month after starting liraglutide	Liraglutide 1.2 mg + metformin 2000 mg daily	8.0%	103 kg
3 months after starting liraglutide	Liraglutide 1.2 mg + metformin 2000 mg daily	5.5%	91 kg
7–8 months after starting liraglutide	Liraglutide 1.2 mg + metformin 2000 mg daily	5%	79 kg
5–6 months after stop taking liraglutide	Metformin 2000 mg daily	5.5%	74 kg
1 years after stop taking liraglutide	Metformin 2000 mg daily	5.3%	75 kg

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in the management of young people with T2DM [20, 11]. Several diabetes prevention trials in adults demonstrate that lifestyle intervention, consisting of increased physical activity and dietary modification with lower caloric intake and weight loss, reduces the rate of progression to T2DM in people with impaired glucose tolerance [21, 22]. However, based on observations in adults, the current recommendation in the management of adolescents with T2DM includes both dietary and exercise modification [1, 10].

Conclusion

The case presented here summarized the benefit of initial treatment for young people with T2DM, the combination of GLP-1 receptor agonist, metformin, and most important the lifestyle changes. The potential benefits of adding GLP-1 receptor agonist to the therapy to metformin include weight loss, improved glycemic control, and enhanced safety in getting the desired results [7]. GLP-1 receptor agonists are especially promising and should be tested in this population without delay [14]. The potential disadvantages are gastrointestinal side effects and the risk of hypoglycemia if the doses of concurrent hypoglycemic medication are not titrated, especially if the weight loss is more than expected [13, 23]. The goals of managing a young patient with T2DM include the following: 1. to achieve and maintain near normal glycemic control, 2. to improve insulin sensitivity and secretion, which results in improved glycemic control [4], 3. to identify and treat, if necessary, comorbidities such as hypertension, dyslipidemia, and nonalcoholic fatty liver disease and 4. to prevent the vascular complication of T2DM [20]. Weight reduction improves glycemic control and is a crucial component of successful management of T2DM in young people [3]. Lifestyle modifications to reduce body weight should be initiated in all patients with this disorder, because weight loss reduces insulin resistance and improves insulin secretion [10, 22].

For initial treatment of the young with T2DM, we recommend both pharmacologic and nonpharmacologic therapy (lifestyle modification) for all patients. Laboratory measurement of glycaemia, HgA1c, should be routinely monitored, and medication type and dose adjusted as needed [11]. Ongoing therapeutic choices are dependent upon the response of patients to the initial therapy. Screening and treatment for diabetes-related comorbidities and complications (hypertension, dyslipidemia, nonalcoholic fatty liver disease, macro and microvascular disease) is essential in preventing early morbidity and mortality, and should be performed once a year [21, 18].

In conclusion, liraglutide is an effective treatment option for obese T2DM patients [17], and it helps in reducing body weight and improving glycemic control without deteriorating QOL [9, 24, 12]. The difficulty in treating T2DM in youth highlights the critical need to promote healthy lifestyle to prevent or postpone the development of T2DM in those at risk [1]. For individuals with early onset T2DM, glycemic control must be carefully monitored and treated. Young adults with diabetes risk factors, such as a family history of diabetes, should be considered for screening of diabetes and metabolic disorders [2, 15].

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IT – writing the manuscript. All authors – design of the study and final approval

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Conflict of Interest

The authors declare no conflict of interest.

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Referințe: 1. Lyumjev® - RCP, ianuarie 2021; **2.** Datye KA. et al. J Diabetes Sci Technol 2018; 12(2):349-355; **3.** Heise T. et al. Diabetes Obes Metab. 2020;1–10.

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Tratamentul cu Lyumjev trebuie întrerupt dacă apar reacţii de hipersensibilitate. **Interacţiuni cu alte medicamente şi alte forme de interacţiune** Următoarele substanţe pot reduce necesarul de insulină: medicamentele antidiabetice (orale sau injectabile), salicilaţii, sulfonamidele, anumite antidepresive (inhibitorii monoaminooxidazei (IMAO), inhibitorii selectivi ai recaptării serotoninei), inhibitorii enzimei de conversie a angiotensinei (ECA), antagoniştii receptorilor de angiotensină II sau analogii somatostatinei. **Fertilitatea, sarcina şi alăptarea** Lyumjev poate fi utilizat pe durata sarcinii dacă este indicat din punct de vedere clinic. Lyumjev poate fi utilizat în perioada alăptării. Insulina lispro nu a indus tulburări de fertilitate în studiile la animal. **Efecte asupra capacităţii de a conduce vehicule şi de a folosi utilaje** Capacitatea pacientului de a se concentra şi de a reacţiona poate să fie afectată ca urmare a hipoglicemiei. **Reacţii adverse** Reacţia adversă cel mai frecvent raportată în timpul tratamentului este hipoglicemia (foarte frecventă). *Frecvente* Reacţii la locul injectării Reacţii alergice *Mai puţin frecvente* Lipodistrofie Erupţie cutanată tranzitorie Prurit Edem Raportarea reacţiilor adverse suspectate Raportarea reacţiilor adverse suspectate după autorizarea medicamentului este importantă. Acest lucru permite monitorizarea continuă a raportului beneficiu/risc al medicamentului. Profesioniştii din domeniul sănătăţii sunt rugaţi să raporteze orice reacţie adversă suspectată prin intermediul sistemului naţional de raportare: Agenţia Naţională a Medicamentului şi a Dispozitivelor Medicale din România, Str. Aviator Sănătescu nr. 48, sector 1, Bucureşti 011478- RO, Tel: + 4 0757 117 259, Fax: +4 0213 163 497, e-mail: adr@anm.ro. **Supradozaj** Supradozajul determină hipoglicemie cu simptomele aferente care includ stări de neliniște, confuzie, palpitaţii, transpiraţii, vărsături şi cefalee. **Lista excipienţilor** Glicerol Clorură de magneziu hexahidrat Metacresol Citrat de sodiu dihidrat Treprostinil sodic Oxid de zinc Apă pentru preparate injectabile Acid clorhidric şi hidroxid de sodiu (pentru ajustarea pH-ului) **Incompatibilităţi** Acest medicament nu trebuie amestecat cu alte tipuri de insulină sau alte medicamente în afara celor menţionate în RCP. **Perioada de valabilitate** Înainte de utilizare: 2 ani. După prima utilizare 28 de zile **Precauţii speciale pentru păstrare** Înainte de utilizare: A se păstra la frigider (2 °C - 8 °C). A nu se congela. Păstrarea după prima utilizare A nu se păstra la temperaturi mai mari de 30 °C. A nu se congela. A nu se păstra la frigider. **Precauţii speciale pentru eliminare şi alte instrucţiuni de manipulare** Lyumjev soluţie trebuie să fie transparent şi incolor. A nu se utiliza dacă este tulbure, colorat sau conţine particule sau aglomerări de particule. Orice medicament neutilizat sau material rezidual trebuie eliminat în conformitate cu reglementările locale. **Deținătorul Autorizației de punere pe piață** Eli Lilly Nederland B.V., Papendorpseweg 83, 3528BJ Utrecht, Olanda. **Numerele Autorizațiilor de punere pe piață** EU/1/20/1422/001-012 **Data primei autorizări** Data primei autorizări: 24 martie 2020. **Data revizuirii textului** Ianuarie 2021. Informaţii detaliate privind acest medicament sunt disponibile pe site-ul Agenţiei Europene a Medicamentului http://www.ema.europa.eu

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Toujeo (insulină glargin 300 unităţi/ml) - Informaţii esenţiale din RCP
Prezentare: Toujeo 300 unităţi/ml SoloStar soluţie injectabilă în stilou injector (pen) preumplut. Toujeo 300 unităţi/ml DoubleStar soluţie injectabilă în stilou injector (pen) preumplut. 1 ml soluţie conţine insulină glargin 300 unităţi. Fiecare stilou injector (pen) SoloStar conţine soluţie injectabilă 1,5 ml, echivalent cu 450 unităţi. Fiecare stilou injector (pen) DoubleStar conţine soluţie injectabilă 3 ml, echivalent cu 900 unităţi. **Indicaţii terapeutice:** Tratamentul diabetului zaharat la adulţi, adolescenţi şi copii începând cu vârsta de 6 ani. **Doze şi mod de administrare**: Toujeo este o insulină bazală, care se administrează o dată pe zi, oricând în timpul zilei, de preferat la aceeaşi oră în fiecare zi. Când este necesar, pacienţii îşi pot administra Toujeo cu cel mult 3 ore înainte de sau la maximum 3 ore după momentul obişnuit de administrare. Schema de administrare a dozei (doza şi momentul administrării) trebuie ajustată în funcţie de răspunsul individual. La pacienţii cu diabet zaharat de tip 1, Toujeo trebuie utilizat o dată pe zi şi trebuie asociat cu o insulină cu acţiune de scurtă durată/rapidă, pentru a asigura necesarul prandial de insulină. La pacienţii cu diabet zaharat de tip 2, doza iniţială recomandată pe zi este de 0,2 unităţi/kg. Toujeo poate fi administrat şi în asociere cu alte medicamente antidiabetice. **Schimbarea tratamentului**: *Schimbarea tratamentului între insulină glargin 100 unităţi/ml şi Toujeo*: Insulina glargin 100 unităţi/ml şi Toujeo nu sunt bioechivalente şi nu sunt interschimbabile direct. În cazul schimbării tratamentului de la insulină glargin 100 unităţi/ml la Toujeo, aceasta se poate efectua unitate la unitate, dar poate fi necesară o doză mai mare de Toujeo (cu aproximativ 10 18%) pentru a atinge valorile glicemiei din intervalul ţintă. În cazul schimbării tratamentului de la Toujeo la insulină glargin 100 unităţi/ml, doza trebuie scăzută (cu aproximativ 20%), pentru a reduce riscul de hipoglicemie. *Schimbarea tratamentului de la alte insuline bazale la Toujeo*: În cazul schimbării tratamentului de la o schemă de tratament care conţine o insulină cu acţiune de durată intermediară sau de lungă durată la o schemă de tratament cu Toujeo, poate fi necesară o modificare a dozei de insulină bazală, precum şi ajustarea tratamentului antidiabetic asociat (doza şi momentul administrării pentru insulinele regular asociate sau pentru analogii de insulină cu acţiune rapidă asociaţi sau doza medicamentelor antidiabetice non-insulinice). Schimbarea tratamentului de la insuline bazale, cu administrare o dată pe zi, la Toujeo administrat o dată pe zi poate fi efectuată unitate la unitate, pe baza dozei anterioare de insulină bazală. În cazul schimbării tratamentului de la insuline bazale cu administrare de două ori pe zi, la Toujeo administrat o dată pe zi, doza iniţială recomandată pentru Toujeo este de 80% din doza zilnică totală de insulină bazală a cărei administare se întrerupe. Pacienţii trataţi cu doze mari de insulină din cauza prezenţei anticorpilor anti-insulină umană pot avea un răspuns îmbunătăţit la insulină în cazul administrării Toujeo. În timpul schimbării tratamentului şi, ulterior, pe parcursul săptămânilor iniţiale, se recomandă supraveghere medicală cu monitorizare metabolică strictă. ***Pentru toate detaliile privind schimbarea tratamentului, citiţi RCP complet***. **Grupe speciale de pacienţi**: Toujeo poate fi utilizat la vârstnici, la pacienţi cu insuficienţă renală şi la pacienţi cu insuficienţă hepatică. La pacienţi cu insuficienţă renală şi la pacienţi cu insuficienţă hepatică, necesarul de insulină poate fi diminuat. Toujeo poate fi utilizat la adolescenţi şi copii începând cu vârsta de 6 ani, pe baza aceloraşi principii ca în cazul pacienţilor adulţi. Atunci când se schimbă tratamentul de la insulină bazală la Toujeo, scăderea dozelor de insulină bazală şi a bolusurilor de insulină trebuie evaluată în mod individual, pentru a reduce la minimum riscul de hipoglicemie. Siguranţa şi eficacitatea Toujeo la copii cu vârsta sub 6 ani nu au fost stabilite. **Mod de administrare:** Se administrează numai pe cale subcutanată. Locurile de administrare a injecţiei din cadrul unei regiuni selectate pentru administrare trebuie alternate de la o injecţie la alta pentru a reduce riscul de lipodistrofie şi de amiloidoză cutanată. Toujeo nu trebuie administrat intravenos sau în pompe de perfuzie pentru insulină. Atunci când se trece de la Toujeo SoloStar la Toujeo DoubleStar, dacă doza anterioară a pacientului a fost un număr impar (de exemplu 23 unităţi), atunci doza trebuie crescută sau scăzută cu 1 unitate (de exemplu la 24 unităţi sau 22 unităţi). Stiloul injector (pen-ul) preumplut Toujeo DoubleStar este recomandat la pacienţii care necesită cel puţin 20 unităţi pe zi. Toujeo nu trebuie extras cu seringa din cartuşul stiloului injector (pen-ului) preumplut Toujeo SoloStar sau al stiloului injector (pen-ului) preumplut Toujeo DoubleStar, deoarece poate rezulta supradozaj sever. Pentru detalii privind administrarea, citiţi RCP complet. **Contraindicaţii:** hipersensibilitate la substanţa activă sau la oricare dintre excipienţi. **Atenţionări şi precauţii:** Pentru a avea sub control trasabilitatea medicamentelor biologice, numele şi numărul lotului medicamentului administrat trebuie înregistrate cu atenţie. Toujeo nu este insulina de elecţie pentru tratamentul cetoacidozei diabetice. Pacienţii trebuie instruiţi să alterneze continuu locurile de injectare, pentru a reduce riscul de apariţie a lipodistrofiei şi amiloidozei cutanate. Există un posibil risc de absorbţie întârziată a insulinei sau de reglare insuficientă a glicemiei în urma injectării insulinei în locuri unde au apărut aceste reacţii. Schimbarea bruscă a locului de injectare cu o zonă neafectată duce la hipoglicemie. Se recomandă monitorizarea glicemiei după schimbarea locului de injectare şi se poate avea în vedere ajustarea dozei de medicament antidiabetic. ***Hipoglicemia:*** Se recomandă prudenţă deosebită şi sporirea supravegherii glicemiei la pacienţii în cazul cărora episoadele hipoglicemice pot avea o relevanţă clinică particulară, cum sunt pacienţii cu stenoză semnificativă a arterelor coronare sau a vaselor sanguine cerebrale (risc de complicaţii cardiace sau cerebrale ale hipoglicemiei), precum şi la pacienţii cu retinopatie proliferativă, mai ales dacă nu au fost trataţi prin fotocoagulare (risc de amauroză tranzitorie consecutivă hipoglicemiei). Pacienţii trebuie atenţionaţi cu privire la circumstanţele în care simptomele de avertizare a hipoglicemiei sunt diminuate. Efectul prelungit al insulinei glargin poate întârzia remiterea hipoglicemiei. ***Afecţiuni intercurente***: necesită intensificarea supravegherii metabolice. ***Anticorpi anti-insulină:*** Administrarea insulinei poate determina formarea de anticorpi anti-insulină. În cazuri rare, prezenţa acestor anticorpi anti-insulină poate face necesară ajustarea dozei de insulină pentru a corecta tendinţa la hiper- sau hipoglicemie. ***Asocierea Toujeo cu pioglitazonă***: Au fost raportate cazuri de insuficienţă cardiacă în cazul utilizării pioglitazonei în asociere cu insulină, mai ales la pacienţii cu factori de risc pentru dezvoltarea insuficienţei cardiace. Acest lucru trebuie avut în vedere dacă se ia în considerare administrarea Toujeo în asociere cu pioglitazona. Dacă este utilizată asocierea, pacienţii trebuie supravegheaţi pentru identificarea de semne şi simptome ale insuficienţei cardiace, creştere în greutate şi edeme. Administrarea pioglitazonei trebuie întreruptă la apariţia oricărei deteriorări a simptomatologiei cardiace. ***Prevenirea erorilor de medicaţie***: Înainte de administrarea fiecărei injecţii, trebuie verificată întotdeauna eticheta insulinei. **Interacţiuni**: Substanţele care pot intensifica (şi creşte susceptibilitatea la hipoglicemie) sau scădea efectul de scădere a glicemiei sunt detaliate în RCP complet. **Fertilitatea, sarcina şi alăptarea:** Nu există experienţă clinică privind utilizarea Toujeo la femeile gravide. Pentru insulina glargin nu sunt disponibile date clinice din studii controlate privind utilizarea sa la femeile gravide. Conform unui număr mare de date privind femeile gravide nu s-au evidenţiat reacţii adverse asupra sarcinii specifice insulinei glargin şi nici efecte malformative sau efecte toxice feto/neo-natale ale insulinei glargin. Utilizarea Toujeo poate fi luată în considerare în timpul sarcinii, dacă este necesar din punct de vedere clinic. Nu se cunoaşte dacă insulina glargin se excretă în laptele uman. Nu se anticipează apariţia de efecte metabolice ale insulinei glargin ingerate asupra nou-născuţilor/sugarilor alăptaţi, deoarece insulina glargin este descompusă în aminoacizi la nivelul tractului gastro-intestinal. **Efecte asupra capacităţii de a conduce vehicule**: Capacitatea de concentrare şi de reacţie a pacientului poate fi afectată din cauza hipoglicemiei, hiperglicemiei sau, de exemplu, din cauza tulburărilor vizuale. Pacienţii trebuie atenţionaţi să îşi ia toate măsurile de precauţie pentru a evita hipoglicemia în timp ce conduc vehicule. **Reacţii adverse:** *Foarte frecvente:* Hipoglicemia. Hipoglicemia poate să apară dacă doza de insulină este prea mare în raport cu necesarul de insulină. Episoadele severe de hipoglicemie, mai ales dacă sunt recurente, pot determina leziuni neurologice. Este posibil ca episoadele hipoglicemice prelungite sau severe să aibă potenţial letal. Frecvente: lipohipertrofie, reacţii la locul de injectare care includ eritem, durere, prurit, urticarie, edem sau inflamaţie. *Cu frecvenţă necunoscută*: amiloidoză cutanată. Lipodistrofia şi amiloidoza cutanată pot întârzia absorbţia insulinei. Pentru toate reacţiile adverse, citiţi RCP complet. La copiii cu vârsta sub 6 ani, nu sunt disponibile date privind siguranţa provenite din studii clinice. Profesioniştii din domeniul sănătăţii sunt rugaţi să raporteze orice reacţii adverse pe www.anm.ro/Raportează o reacţie adversă. **Supradozaj:** Episoadele uşoare de hipoglicemie pot fi tratate, de obicei, prin administrarea orală de glucide. Episoadele mai severe pot fi tratate prin administrare de glucagon intramuscular/subcutanat sau de soluţie concentrată de glucoză intravenos. Pot fi necesare aportul susţinut de glucide şi menţinerea sub observaţie a pacientului, deoarece hipoglicemia poate să reapară după o ameliorare clinică aparentă. **DAPP**: Sanofi-Aventis Deutschland GmbH **Mod de eliberare:** prescripţie medicală PRF. **Text revizuit la data de**: februarie 2021, bazat pe RCP revizuit în iulie 2020. ***Pentru informaţii complete de prescriere, citiţi Rezumatul caracteristicilor produsului.***
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▼ Acest medicament face obiectul unei monitorizări suplimentare. Acest lucru va permite identificarea rapidă de noi informaţii referitoare la siguranţă. Profesioniştii din domeniul sănătăţii sunt rugaţi să raporteze orice reacţii adverse suspectate.

Suliqua (insulină glargin 100 unităţi/ml / lixisenatidă): Informaţii esenţiale din RCP

Prezentare: Suliqua 100 unităţi/ml + 50 micrograme/ml soluţie injectabilă în stilou injector (pen) preumplut. Fiecare stilou injector (pen) preumplut conţine insulină glargin 300 unităţi şi lixisenatidă 150 micrograme în 3 ml soluţie. Suliqua 100 unităţi/ml + 33 micrograme/ml soluţie injectabilă în stilou injector (pen) preumplut. Fiecare stilou injector (pen) preumplut conţine insulină glargin 300 unităţi şi lixisenatidă 100 micrograme în 3 ml soluţie. Fiecare ml conţine metacrezol 2,7 miligrame. **Indicaţii terapeutice:** Suliqua este indicat la adulţi pentru tratamentul diabetului zaharat de tip 2 insuficient controlat, pentru a îmbunătăţi controlul glicemic, ca adjuvant dietei şi exerciţiului fizic, adăugat la metformină administrată în asociere cu sau fără inhibitori ai co-transportorului 2 de sodiu glucoză (SGLT-2). **Doze şi mod de administrare**: Suliqua este disponibil sub formă de două stilouri injectoare (pen-uri); Suliqua 100 unităţi/ml + 50 micrograme/ml stilou injector (pen) preumplut eliberează doze în trepte cuprinse între **10-40 unităţi** insulină glargin, în combinaţie cu **5-20 µg** lixisenatidă (pen-ul Suliqua (10-40)). Suliqua 100 unităţi/ml + 33 micrograme/ml stilou injector (pen) preumplut eliberează doze în trepte cuprinse între **30-60 unităţi** insulină glargin, în combinaţie cu **10-20 µg** lixisenatidă (pen-ul Suliqua (30-60)). Pentru a evita erorile de medicaţie, medicul prescriptor trebuie să se asigure că sunt menţionate în prescripţie concentraţia corectă şi numărul corect de trepte de dozare. Doza trebuie stabilită în mod individual, pe baza răspunsului clinic, şi se ajustează treptat, în funcţie de necesarul de insulină al pacientului. *Doza iniţială*: Tratamentul cu insulina bazală sau cu agonistul receptorului pentru peptidul 1 asemănător glucagonului (glucagon like peptide-1 (GLP-1)) sau cu un medicament antidiabetic oral, altul decât metformina şi inhibitorii SGLT-2, trebuie întrerupt înainte de iniţierea administrării de Suliqua. Doza iniţială de Suliqua se bazează pe tratamentul antidiabetic anterior şi pe recomandarea de a nu depăşi doza iniţială recomandată pentru lixisenatidă de 10 µg:

		Tratament anterior		
		Pacienţi netrataţi cu insulină (Tratament antidiabetic oral sau cu un agonist al receptorului GLP-1)	**Insulină glargin (100 unităţi/ml)** ≥20 şi <30 unităţi**	**Insulină glargin (100 unităţi/ml)** ≥30 şi ≤60 unităţi**
Doza iniţială şi stiloul injector (pen-ul)	**Stiloul injector (pen-ul) Suliqua (10-40)**	10 trepte de dozare (10 unităţi/5 µg)*	20 trepte de dozare (20 unităţi/10 µg)*	
	Stiloul injector (pen-ul) Suliqua (30-60)			30 trepte de dozare (30 unităţi/10 µg)*

* unităţi insulină glargin (100 unităţi/ml)/µg lixisenatidă

** *Dacă se utilizează o insulină bazală diferită*: Pentru insulina bazală administrată de două ori pe zi sau pentru insulina glargin (300 unităţi/ml), doza totală zilnică utilizată anterior trebuie scăzută cu 20% pentru a selecta doza iniţială de Suliqua. Pentru orice altă insulină bazală, trebuie aplicată aceeaşi regulă ca în cazul insulinei glargin (100 unităţi/ml). Doza zilnică maximă este de 60 unităţi de insulină glargin şi 20 µg lixisenatidă, ceea ce corespunde la 60 trepte de dozare. Suliqua trebuie injectat o dată pe zi, în ora de dinaintea unei mese. Este preferabil ca injecţia să fie efectuată în fiecare zi înainte de aceeaşi masă, după ce a fost aleasă cea mai convenabilă masă. *Ajustarea dozei*: Doza de Suliqua se stabileşte în conformitate cu necesarul de insulină al fiecărui pacient în parte (pentru detalii, vezi pct. 4.2 din RCP complet). *Grupe speciale de pacienţi: Vârstnici* (≥65 ani) Suliqua poate fi utilizat. Doza trebuie ajustată în mod individual, pe baza monitorizării glicemiei. Deteriorarea progresivă a funcţiei renale poate duce la scăderea constantă a necesarului de insulină. Experienţa terapeutică este limitată la ≥75 ani. *Insuficienţă renală*: Suliqua nu este recomandat la pacienţii cu insuficienţă renală severă şi cu afecţiune renală în stadiu terminal. Nu este necesară ajustarea dozei de lixisenatidă la pacienţii cu insuficienţă renală uşoară sau moderată. La pacienţii cu insuficienţă renală, necesarul de insulină poate fi diminuat şi pot fi necesare monitorizarea frecventă a glicemiei şi ajustarea dozei. *Insuficienţă hepatică*: Nu este necesară ajustarea dozei de lixisenatidă. Necesarul de insulină poate fi diminuat şi pot fi necesare monitorizarea frecventă a glicemiei şi ajustarea dozei. *Copii şi adolescenţi*: Suliqua nu prezintă utilizare relevantă la copii şi adolescenţi. *Mod de administrare*: Suliqua trebuie injectat subcutanat, la nivel abdominal, deltoidian sau al coapsei. Locurile de injectare trebuie alternate în cadrul aceleiaşi regiuni (abdomen, deltoid sau coapsă) de la o injecţie la alta, pentru a scădea riscul de lipodistrofie şi amiloidoză cutanată. Pacienţii trebuie instruiţi să utilizeze întotdeauna un ac nou. Suliqua nu trebuie extras cu seringa din cartuşul stiloului injector (pen-ului) preumplut, pentru a evita erorile de administrare şi un potenţial supradozaj. Vezi RCP complet pentru toate informaţiile. **Contraindicaţii**: Hipersensibilitate la substanţele active sau la oricare dintre excipienţi. **Atenţionări şi precauţii:** Pentru a avea sub control trasabilitatea medicamentelor biologice, numele şi numărul lotului medicamentului administrat trebuie înregistrate cu atenţie. Suliqua nu trebuie utilizat la pacienţii cu diabet zaharat de tip 1 sau pentru tratamentul cetoacidozei diabetice. Pacienţii trebuie instruiţi să alterneze continuu locurile de injectare, pentru a reduce riscul de apariţie a lipodistrofiei şi amiloidozei cutanate. Există un posibil risc de absorbţie întârziată a insulinei sau de reglare insuficientă a glicemiei în urma injectării insulinei în locuri unde au apărut aceste reacţii. Schimbarea bruscă a locului de injectare cu o zonă neafectată duce la hipoglicemie. Se recomandă monitorizarea glicemiei după schimbarea locului de injectare şi se poate avea în vedere ajustarea dozei de medicament antidiabetic. Hipoglicemia poate apărea dacă doza de Suliqua este mai mare decât este necesar; doza trebuie stabilită individual, pe baza răspunsului clinic. Au fost raportate câteva evenimente de pancreatită acută pentru lixisenatidă, cu toate că nu a fost stabilită o relaţie de cauzalitate. Pacienţii trebuie informaţi despre simptomele caracteristice: durere abdominală severă, persistentă. Dacă este suspectată pancreatita, trebuie întrerupt tratamentul cu Suliqua; dacă pancreatita acută se confirmă, nu trebuie reîncepută administrarea lixisenatidei. Este necesară prudenţă la pacienţii cu antecedente de pancreatită. Suliqua nu este recomandat la pacienţii cu afecţiuni gastro-intestinale severe, inclusiv gastropareză severă. Este necesară precauţie la pacienţii trataţi cu medicamente administrate oral care necesită o absorbţie gastro-intestinală rapidă, supraveghere clinică atentă sau care au un indice terapeutic îngust (pentru detalii, vezi pct. 4.5 din RCP complet). Sfătuiţi pacienţii să ia măsuri de precauţie pentru a se evita depleţia de lichide. În cazuri rare, prezenţa de anticorpi poate face necesară ajustarea dozei de Suliqua. Pacienţii trebuie instruiţi să verifice întotdeauna eticheta stiloului injector (pen-ului) înainte de fiecare injecţie. Suliqua nu a fost studiat în asociere cu inhibitori ai dipeptidil peptidazei 4, medicamente sulfonilureice, glinide, pioglitazonă. Acest medicament conţine metacrezol, care poate provoca reacţii alergice. **Interacţiuni**: Nu s-au efectuat studii privind interacţiunile cu Suliqua. Informaţiile prezentate în RCP complet se bazează pe studii cu fiecare componentă în parte (vezi pct. 4.5 din RCP complet pentru toate detaliile). **Fertilitatea, sarcina şi alăptarea**: Nu este recomandat la femeile aflate la vârsta fertilă care nu utilizează măsuri de contracepţie. Suliqua nu trebuie utilizat în timpul sarcinii sau al alăptării. **Efecte asupra capacităţii de a conduce vehicule**: Suliqua nu are nicio influenţă sau are influenţă neglijabilă asupra capacităţii de a conduce vehicule sau de a folosi utilaje. Pacienţii trebuie sfătuiţi să-şi ia măsuri de precauţie pentru a evita hipoglicemia în timp ce conduc vehicule şi folosesc utilaje. **Reacţii adverse**: Reacţiile adverse raportate cel mai frecvent în timpul tratamentului cu Suliqua au fost hipoglicemia şi reacţiile adverse gastro-intestinale. Din studii clinice: Foarte frecvente: hipoglicemie. Frecvente: ameţeli, greaţă, diaree, vărsături, reacţii la nivelul locului de injectare. Pentru reacţiile adverse apărute mai puţin frecvent, rar, foarte rar sau cu frecvenţă necunoscută, citiţi RCP complet. Pentru modul de raportare a reacţiilor adverse, vezi www.anm.ro/Raportează o reacţie adversă. **DAPP**: sanofi-aventis groupe **Mod de eliberare**: pe bază de prescripţie medicală PRF. **Data primei autorizări**: 11 ianuarie 2017. **Text revizuit la data de**: ianuarie 2021, bazat pe RCP revizuit în iulie 2020. *Pentru informaţii complete de prescriere, citiţi Rezumatul caracteristicilor produsului.*

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Jardiance® (empagliflozin) comprimate filmate 10 mg, 25 mg. Indicații terapeutice: tratamentul adulților cu diabet zaharat tip 2 insuficient controlat, ca adjuvant la dietă și exercițiul fizic: ca monoterapie atunci când metformina este considerată inadecvată din cauza intoleranței; în plus față de alte medicamente pentru tratamentul diabetului zaharat. **Doze și mod de administrare:** Doza inițială este de 10 mg o dată pe zi (în monoterapie și în terapie asociată suplimentară cu alte medicamente pentru tratamentul diabetului zaharat). La pacienții care tolerează empagliflozin 10 mg o dată pe zi, care prezintă RFGe ≥60 ml/min/1,73 m^2 și care necesită un control glicemic mai strict, doza poate fi crescută la 25 mg o dată pe zi. Doza zilnică maximă este de 25 mg. Când empagliflozin este utilizat în asociere cu o sulfoniluree sau cu insulină, se poate avea în vedere o doză mai mică de sulfoniluree sau de insulină, pentru a reduce riscul de hipoglicemie. IR Nu este necesară ajustarea dozei la pacienți cu RFGe ≥60 ml/min/1,73 m^2 sau ClCr ≥60 ml/min. Administrarea nu trebuie inițiată la pacienți cu RFGe <60 ml/min/1,73 m^2 sau ClCr <60 ml/min. La pacienții la care valorile RFGe scad în mod persistent sub 60 ml/min/1,73 m^2 sau ClCr sub 60 ml/min, doza trebuie ajustată sau menținută la 10 mg o dată pe zi. Administrarea trebuie întreruptă la pacienții cu valori ale RFGe aflate persistent sub 45 ml/min/1,73 m^2 sau cu valori ale ClCr aflate persistent sub 45 ml/min. Nu trebuie utilizat la pacienții cu BRST sau cărora li se efectuează dializă. IH Nu este necesară ajustarea dozei la pacienți cu IH. Nu se recomandă utilizarea la pacienți cu IH severă. Vârstnici La pacienții cu vârsta de 75 ani și peste, trebuie avut în vedere un risc crescut de depleție volemică. Nu se recomandă începerea tratamentului cu empagliflozin la pacienții cu vârsta de 85 ani și peste. Copii și adolescenți La acest grup de pacienți, siguranța și eficacitatea administrării empagliflozin nu au fost încă stabilite. Nu sunt disponibile date. Mod de administrare Comprimatele pot fi administrate cu sau fără alimente, înghițite întregi cu apă. Dacă se omite o doză, aceasta trebuie administrată imediat ce pacientul își aduce aminte. În aceeași zi nu trebuie administrată o doză dublă. **Contraindicații:** Hipersensibilitate la substanța activă sau la oricare dintre excipienți. **Atenționări și precauții speciale pentru utilizare:** Au fost raportate cazuri rare de CAD, inclusiv cazuri cu risc vital și cazuri letale la pacienți tratați cu inhibitori de SGLT2, inclusiv empagliflozin. Într-o serie de cazuri, natura afecțiunii a fost atipică, cu valori ale glicemiei mai mici de 14 mmol/l (250 mg/dl). Nu se cunoaște dacă CAD are o probabilitate mai mare de apariție în cazul utilizării dozelor mai mari de empagliflozin. Riscul de CAD trebuie luat în considerare în cazul apariției unor simptome nespecifice. Pacienții trebuie evaluați pentru depistarea CAD imediat ce apar aceste simptome, indiferent de valorile glicemiei. La pacienții unde se suspectează sau este diagnosticată CAD, tratamentul trebuie întrerupt imediat. Tratamentul trebuie întrerupt la pacienții spitalizați pentru efectuarea intervențiilor chirurgicale majore sau care au afecțiuni acute severe. Tratamentul poate fi reluat după ce starea pacientului se stabilizează. Înainte de a iniția tratamentul, trebuie luate în considerare antecedentele pacientului care pot predispune la CAD. Nu se recomandă reluarea tratamentului cu inhibitor de SGLT2 la pacienții cu antecedente de CAD dezvoltată în timpul tratamentului cu inhibitor de SGLT2 decât dacă a fost identificat și rezolvat un alt factor precipitant evident. Jardiance nu trebuie utilizat pentru tratarea pacienților cu diabet zaharat de tip 1. Datele provenite dintr-un program de studii clinice privind diabetul zaharat de tip 1 au arătat o creștere a incidenței CAD, care apare frecvent la pacienții cărora li se administrează empagliflozin 10 mg și 25 mg ca adjuvant la insulină, comparativ cu placebo. Monitorizarea funcției renale: înainte de începerea tratamentului și periodic în timpul tratamentului, cel puțin anual; Înainte de începerea tratamentului concomitent cu orice medicament care poate avea impact negativ asupra funcției renale. Leziuni hepatice Cazuri de leziuni hepatice au fost raportate atunci când s-a administrat empagliflozin în cadrul studiilor clinice. Nu s-a stabilit o relație de cauzalitate între empagliflozin și leziunea hepatică. Risc de depleție volemică Se impune prudență la pacienții la care scăderea tensiunii arteriale indusă de empagliflozin ar putea prezenta un risc. Până la corectarea pierderii de lichide, se va avea în vedere întreruperea temporară a tratamentului cu empagliflozin. Infecții ale căilor urinare În cadrul unor studii cumulate controlate cu placebo, frecvența infecțiilor căilor urinare raportate a fost similară la pacienții cărora li s-a administrat tratament cu empagliflozin 25 mg și placebo și mai mare la pacienții cărora li s-a administrat tratament cu empagliflozin 10 mg. La pacienții cărora li s-a administrat tratament cu empagliflozin s-au raportat ulterior punerii pe piață cazuri de infecții complicate ale căilor urinare. Întreruperea temporară a tratamentului cu empagliflozin trebuie avută în vedere la pacienții cu infecții complicate ale căilor urinare. Fasceită necrozantă care afectează perineul (gangrena Fournier) După punerea pe piață, s-au raportat cazuri de fasceită necrozantă care afectează perineul (afecțiune cunoscută și ca gangrena Fournier) la pacienți de ambele sexe tratați cu inhibitori de SGLT2. Este un eveniment rar, însă grav, care poate pune în pericol viața și care necesită intervenție chirurgicală urgentă și tratament cu antibiotice. În cazul în care există suspiciunea de gangrenă Fournier, se va întrerupe administrarea Jardiance și se va institui imediat tratament (inclusiv antibiotice și debridare chirurgicală). IC Experiența la pacienți cu clasa NYHA I-II este limitată; nu există experiență în studiile clinice cu empagliflozin la pacienți cu clasa NYHA III-IV. În cadrul studiului EMPA-REG OUTCOME, la 10,1% dintre pacienți s-a raportat insuficiență cardiacă la momentul inițial. Scăderea numărului de decese de etiologie cardiovasculară la acești pacienți a fost similară cu cea înregistrată la populația de studiu totală. Evaluarea analizelor de laborator ale urinei Pacienții care urmează tratament cu Jardiance vor avea glicozurie pozitivă. Lactoză Comprimatul conține lactoză. Pacienții cu afecțiuni ereditare rare de intoleranță la galactoză, deficit de lactază Lapp sau sindrom de malabsorbție a glucozei-galactozei nu trebuie să utilizeze acest medicament. **Fertilitatea, sarcina și alăptarea:** Datele provenite din utilizarea empagliflozinului la gravide sunt inexistente. Este de preferat să se evite utilizarea Jardiance în timpul sarcinii. Nu trebuie utilizat în timpul alăptării. Nu s-au efectuat studii privind efectele Jardiance asupra fertilității la om. Studiile la animale nu au evidențiat efecte dăunătoare directe sau indirecte cu privire la fertilitate. **Efecte asupra capacității de a conduce vehicule și de a folosi utilaje:** Jardiance are influență mică asupra capacității de a conduce vehicule și de a folosi utilaje. Pacienții trebuie sfătuiți să ia măsuri de precauție pentru a evita hipoglicemia atunci când conduc vehicule și folosesc utilaje, în special atunci când Jardiance este utilizat în asociere cu o sulfoniluree și/sau insulină. **Reacții adverse (RA):** Siguranța administrării empagliflozinului a fost evaluată la un număr total de 15582 pacienți cu diabet zaharat de tip 2 incluși în studiile clinice. Reacția adversă raportată cel mai frecvent a fost hipoglicemia, atunci când se asociază cu sulfoniluree sau insulină. *Foarte frecvente:* hipoglicemie (atunci când se utilizează împreună cu sulfoniluree sau insulină). *RA frecvente:* candidoză vaginală, vulvovaginită, balanită și alte infecții genitale; infecții ale căilor urinare, sete, prurit, erupție cutanată tranzitorie, diureză crescută, creștere a lipidelor serice. *RA mai puțin frecvente:* urticarie, depleție volemică, disurie, creșterea creatininei sanguine/scăderea ratei de filtrare glomerulară, creșterea hematocritului. *RA rare:* CAD; *cu frecvența necunoscută:* angioedem, fasceită necrozantă care afectează perineul (gangrena Fournier). **Data ultimei reînnoiri a autorizației:** 14/02/2019. **Data revizuirii textului:** 09/2020. **Acest material promoțional este destinat profesioniștilor din domeniul sănătății. Jardiance® se eliberează pe bază de prescripție medicală PRF. Pentru informații suplimentare vă rugăm să consultați RCP complet, disponibil la cerere.**

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Referințe: 1. JARDIANCE Rezumatul Caracteristicilor Produsului, septembrie 2020 2. Zinman B, Inzucchi S, Lachin JM, et al. EMPA-REG OUTCOME® Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular aoutcome trial of empagliflozin. Cardiovasc Diabetol. 2014;13(102):1-8.

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